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GASTRIC ACIDITY AND ACID THERAPY IN ALLERGY*

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THIS investigation was conducted to test the validity of the claim that a connection exists between allergy and gastric hypoacidity, and to test the worth of acid therapy.

The association of low acidity with various allergic conditions has been found by numerous workers: Ehrmann,[1, 2] Urbach,[3] Csillag,[4] Barber and his coworkers,[5] Duke,[6] Criep and McElroy,[7] Rowe,[8] Hurst,[9] Knott and his coworkers,[10] Criep and Wechsler.[11] Bray[12, 13] has reported the gastric analyses of 200 asthmatic children, 80 per cent of whom were below normal in free acid.

When Hemingway[14] subjected isolated smooth muscle rings to changes in hydrogen ion concentration, he found that there was an increasing reaction (constriction) as the alkalinity increased. In line with this, McConnell and his coworkers[15] showed that experimental alkalosis of the blood stream increased the size of the histamine wheal, whereas acidosis markedly diminished its size.

Benefit of varying magnititude has been attributed to the use of different forms of acid therapy in allergic cases by such men as Criep and McElroy,[7] Peshkin and Fineman,[16] Beckman,[17] Scheer,[18] and Barborka.[19] Tiefensee[20] studied the acid-base balance of asthmatic individuals and found that there was a shift toward alkalosis during attacks; acid therapy was distinctly beneficial. Bray[12, 13] advocates the acid therapy highly, giving his patients large therapeutic doses of dilute hydrochloric acid over a period of several months, with striking benefits which continue even after medication has ceased. Bray had been prescribing the acid therapy for eighteen months at the time of his publication,[12] and stated that the majority of patients treated had remained symptom free for a year.

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Not all workers have, however, confirmed the above findings. Szour[21] was, for instance, unable to duplicate the clinical benefits of Tiefensee's acidifying diet, and his studies on the acid-base status of untreated asthmatic individuals revealed a tendency toward acidosis during paroxysms. He procured more relief with alkali therapy than with acidifying salts. He decided that acid-base changes in asthma, if they occur, are strictly complications and not fundamental; that no acid-base aids are indicated in simple asthma.

Vallery-Radot and his coworkers[22] and McCaskey[23] found low alkali reserves in urticarial cases, and alkali therapy proved effectual. Alexander[24] prescribed the ketogenic diet for adult asthmatic persons, and concluded that "in no case did ketosis have a pronounced beneficial effect on the severity or duration of asthmatic paroxysms." Criep[25] studied the alkali reserve in urticarial cases and reported: "Laboratory methods fail to reveal any constant changes in this respect; furthermore, neither alkali nor acid therapy is consistently followed by any remarkable results."

Vanzant, Alvarez, Berkson and Eusterman[26] have recently observed the gastric acidity findings in 34 men and 43 women suffering from various allergic complaints. It was found that the mean free acid of allergic men was lower than normal by an average of 3.6 clinical units (c.u.),* whereas that of women was higher than normal by about the same figure. The incidence of achlorhydria was less than that in normal adults. In their 237 cases of migraine, the free acid was only 0.7 c.u. below normal in men, and 2.4 c.u. high in women; whereas the incidence of achlorhydria was normal in migrainous women and definitely less than normal in the male group.

PRESENT STUDY

In the present study every effort has been made to ascertain and control factors which may have contributed to the variant findings of other investigators.

A group of 138 patients under treatment in our allergy clinic were subjected to gastric extraction. Among these patients there were 98 with asthma, 68 with vasomotor rhinitis, 31 with hay fever, 16 with urticaria or angioneurotic edema, 13 with eczema, 5 with gastrointestinal symptoms which were definitely allergic, 2 with heat and cold sensitivity, 2 with migraine, and 1 with allergic purpura. The cases divided themselves into 47 women and 22 men (a total of 69) above the age of twenty years; and 22 girls and 47 boys (a total of 69) below the age of twenty years. Following gastric analysis, patients who were not improving under previously instituted allergic therapy were placed in addition upon hydrochloric acid treatment.

*A clinical unit represents the number of cubic centimeters of tenth-normal sodium hydroxide required to neutralize 100 c.c. of gastric juice.

Dilute hydrochloric acid, U.S.P., in a dosage of 4 c.c. t.i.d. was prescribed for adults, and half this dose for children. These doses were taken not only by patients with achlorhydria and hypochlorhydria, but also by individuals with normal acidity as well as those with hyperacidity. During and after the acid regime, urine and blood studies were made on some of the patients, in order to ascertain the status of the acid-base balance.

Standards for Normal Gastric Acidity.—As a basis for comparison, the range of normal gastric acidity recently established by Vanzant, Alvarez, Eusterman, Dunn and Berkson[27] has been used. Henceforth, this will be referred to as the Vanzant standard. In addition, three other standards of normal have been utilized in the case of children; namely, that of Wright,[28] that of Bray,[12] and one which I constructed in the course of the present study. These standards are based upon normal children from the Middle West, London, and the Atlantic seaboard, respectively, and should eliminate the possibility of geographic influence suggested by Bray.[29]

Technic.—A single extraction was done one hour after the ingestion of an Ewald meal of 35 grams of decrusted and dehydrated white bread; 380 c.c. of water were taken with the bread if the subject was an adult, and 190 c.c. if a child. A Lockwood tube of suitable size was used for extraction because it offers sufficient stiffness for quick, passive introduction and yet is slender enough for relative comfort to the patient without sacrificing efficient transmission of contents. When necessary, gentle suction was made with a rubber bulb. One or two minutes were usually sufficient for the entire procedure, from introduction of the tube to its removal. The stomach was emptied as completely as possible. In almost every case there was sufficient filtrate to permit of at least two titrations of 10 c.c. each. The customary Töpfer's and phenolphthalein dyes were used in titrating the free and total acid, respectively, and results are expressed in terms of the clinical unit (c.u.).

In the following paragraphs and tables, cases with achlorhydria have not been included along with the rest but have been considered separately, comparison being made with normal incidence in terms of per cent.[27]

GASTRIC FINDINGS IN ALLERGIC INDIVIDUALS

Free Acidity in 138 Allergic Adults and Children.—The 20 men in my allergic group averaged a free acidity of 35.2 c.u., which is 9.7 c.u. below the comparable Vanzant figure for normal men. Total acidity for these men averaged 52.4 c.u., which is 7.5 c.u. lower than the mean given by the Vanzant standard for men of comparable age. A study of Table I will show that the male adult group was the only one to fall below normal in acidity.

The 43 allergic women having free acid had a mean of 35.9 c.u., an increase over normal of 3.1 c.u. according to Vanzant figures. Total acid averaged 55.3 c.u., being higher than normal by 5.1 c.u. (Findings for total acidity roughly paralleled those for free acidity, and consequently will not be referred to hereafter.)

TABLE I

GASTRIC FREE ACIDITY IN 132 ALLERGIC PERSONS OF ALL AGES COMPARED WITH VANZANT STANDARD OF NORMAL

"C" (AUTHOR'S ALLERGIC GROUP)	AGE RANGE OF GROUP	FREE ACID (MEAN) OF ALLERGIC GROUP	FREE ACID (MEAN) OF NORMAL PERSONS	"D" (DEVIATION* FROM NORMAL)	("C" × "D") WEIGHTED DEVIATION
20 men	20 to 74	35.2 c.u.	44.9 c.u.	− 9.7 c.u.	−194.0
43 women	20 to 55	35.9 c.u.	32.8 c.u.	+ 3.1 c.u.	+133.3
22 girls	4 to 19	36.0 c.u.	24.3 c.u.	+11.7 c.u.	+257.4
47 boys	3 to 19	43.2 c.u.	27.7 c.u.	+15.5 c.u.	+728.5
132 cases					+925.2

+ 925.2 ÷ 132 = 7.0 c.u. average weighted deviation.

*To obtain the "deviation from normal," the free acid in clinical units for each allergic patient was compared with the (mean) free acid for normal individuals of the same sex and age. The + and − figures thus obtained were then added algebraically; and the sum obtained was divided by the number of cases in the group. The result is the mean deviation for the group in question.

Free acidity in 22 allergic girls was 11.7 c.u. high, with a mean free acid of 36 units. The 47 boys studied had an average free acid of 43.2 c.u., being 15.5 units increased over the Vanzant normal.

When the figures for the 132 cases with free acid were averaged after weighting, they showed an increase over normal of 7.0 c.u. in free acid. The significance of this figure is clearer if one recalls that Vanzant and her coworkers[26] found an increase of 12 units in the free acid of patients with duodenal ulcer. Our allergic patients, therefore, not only failed to show lowered acidity but were on the whole definitely above normal.

Achlorhydria.—In addition to the 132 cases in which free acid was found, there were six cases of achlorhydria among the allergic patients. Two of these were men, while four were women. When repeat alcohol meal tests[30] were given these patients, one woman was found to produce a small amount of hydrochloric acid and was thus classified as apparent achlorhydria. Among the six achlorhydric patients, there was one woman who was achylic, having no pepsin. Each of the achlorhydria patients was given a thorough physical and laboratory study, eliminating the possibility of carcinoma, pernicious anemia, etc. The incidence of true achlorhydria, according to the Vanzant scale,[31] for women between twenty and sixty years averages 10 per cent; whereas in our 47 allergic women between these ages the incidence was 6.3 per cent—definitely less than normal. The incidence of apparent achlorhydria was 2 per cent among our women, whereas 13 per cent is allowed in the scale for normal women. The

incidence of true achlorhydria in normal men averages 10.9 per cent, and among our allergic men it was found in 9 per cent. Since no case of absent free acid was found among our patients of less than twenty years, and since incidence in adult allergic individuals was under normal, our cases failed to confirm the findings of several investigators[5-12] who found definite increase in percentage of achlorhydric cases among allergic individuals.

Comparisons With the Wright Standard for Normal Children.—C. B. Wright[28] has published a standard for normal children between the ages of six and seventeen years, having analyzed the gastric contents of 250 school children with approximately the same technic of extraction as was used in the present study.

Comparing the free acid reading for each allergic person with the normal for that sex and age, it was found that our allergic girls between six and seventeen years, inclusive, averaged 10.2 units higher than the Wright children. This is shown in Table II. Compared with the mean acidity given in the Vanzant range, this same group of girls averaged 11.6 units high. (This calculation is included because the age range covered by the Wright standard differs from that of the Vanzant.)

TABLE II

GASTRIC FREE ACIDITY IN ALLERGIC CHILDREN COMPARED WITH WRIGHT'S STANDARD FOR NORMAL

AUTHOR'S ALLERGIC GROUP	AGE RANGE OF GROUP	FREE ACID (MEAN) OF ALLERGIC GROUP	NORMAL FREE ACID (MEAN) WRIGHT	DEVIATION OF ALLERGIC GROUP FROM WRIGHT NORMAL	DEVIATION OF ALLERGIC GROUP FROM VANZANT NORMAL
39 boys	6 to 17 years	36.6 c.u.	28.5 c.u.	+18.1 c.u.	+18.4 c.u.
18 girls	6 to 17 years	36.7 c.u.	26.5 c.u.	+10.2 c.u.	+11.6 c.u.

Allergic boys between six and seventeen years numbered 39 in our group, and showed an even greater upward deviation from normal in acidity, their mean being 18.1 c.u. over that of Wright's well school boys. Using Vanzant figures as a criterion, these same allergic boys were 18.4 units higher than normal.

Comparisons With the Bray Standard for Normal Children.—Bray analyzed 50 well children and considers 20 to 30 units normal for free acid. Using 30 c.u. as maximal normal, our allergic girls under fourteen years of age (15 in number) were found to be 7.7 c.u. high, having an average free acidity of 37.7 units. Allergic boys under fourteen years of age (43 in number) had also high figures for free acid, averaging 12.9 units above the upper limit of Bray's range. This is shown in Table III.

In contrast to Bray's finding that asthmatic children show subnormal gastric acidity in 80 per cent of cases, the allergic children studied

here showed low acidities, under 20 c.u., in only 6.8 per cent of cases. Hypochlorhydria was found in only 3 boys of 47 tested who were under fourteen years of age (and in one more under twenty years). Of the 22 girls, only one had less than 20 units of free acid, this being a child of six years with 12 c.u.

TABLE III

GASTRIC FINDINGS IN ALLERGIC CHILDREN COMPARED WITH BRAY STANDARD OF NORMAL

AUTHOR'S ALLERGIC GROUP	AGE RANGE OF ALLERGIC GROUP	FREE ACID (MEAN) OF ALLERGIC GROUP	FREE ACID (UPPER LIMIT) OF BRAY NORMAL	DEVIATION OF OUR ALLERGIC PATIENTS FROM NORMAL	ALLERGIC PATIENTS BELOW 20 C.U.	
43 boys	3 to 13 inclusive	42.9 c.u.	30 c.u.	+12.9 c.u.	3 cases	6.8%
15 girls	3 to 13 inclusive	37.7 c.u.	30 c.u.	+ 7.7 c.u.	1 case	

Group of Normal Children in the Vicinity of New York.—To eliminate the possibility of a regional variation in normal gastric acidity, and also as a check against the technic used with our allergic children, a number of youngsters in the vicinity of New York City were subjected to gastric study. These children ranged from three to ten years of age and were 18 in number. They were being kept at a county hospital* for a prolonged period of observation because of a history of exposure to tuberculosis. Of the 18 children, 11 were well, beyond any question, this diagnosis being based upon excellent medical investigation as well as the fact they had been symptom free and fever free for weeks prior to the gastric extraction. This group of 11 will be called, for purpose of distinction, Group A. Group B consisted of apparently well children who had obscure or healed tuberculosis.

Comparison of Allergic With Group A Normal Children.—Among our allergic group there were 30 boys whose ages ranged from three to ten years, this being the age range of our normal boys. The mean free acid for the Group A boys was found to be 24.6 c.u. The corresponding figure for the allergic group was 13.5 c.u. higher.

Compared with the Vanzant standard, our Group A well boys averaged only 2.5 c.u. higher than the normal. According to Wright's data, these same boys were 6.0 c.u. below normal, inasmuch as Wright's figures for normal are rather higher than Vanzant's. Our normal group fell, at any rate, fairly well between the figures in the Vanzant and those in the Wright standards.

Group A well girls of unquestionable health had a free acid averaging 23.5 c.u., almost the same as for Group A boys. Using this well group for comparison, the allergic girls of corresponding ages were

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found to be 11.6 units above normal. Using the other standards of normal as criteria, the Group A girls averaged 7.9 c.u. above the Vanzant and 1.9 c.u. above Wright figures. The mean free acidity of 23.5 c.u. for the normal girls compared favorably with the range used by Bray (20 c.u. to 30 c.u.).

Comparison With Group B Normal Children.—The 8 children in this group had been thoroughly examined (including x-ray) because of a history of contact with tuberculosis. They were symptom free, well nourished, and to all appearances well although diagnosed as having healed or obscure tuberculosis. It was interesting to discover that, despite the reputed hypochlorhydric effect of tuberculosis, each of these children had acidities higher than the nontuberculous group.

Table IV makes a comparison between the allergic children and Group A and B normal children. The allergic boys were 10 c.u. higher in gastric free acid than the normal boys of the same age; whereas allergic girls were 6.7 c.u. higher than the normal ones.

TABLE IV

GASTRIC ACIDITY IN ALLERGIC CHILDREN COMPARED WITH AUTHOR'S GROUP OF NORMAL CHILDREN IN NEW YORK

AUTHOR'S ALLERGIC GROUP	AGE RANGE OF GROUP	FREE ACID (MEAN) IN ALLERGIC GROUP	FREE ACID IN GROUP A AND B NORMAL CHILDREN	DEVIATION OF ALLERGIC CHILDREN FROM GROUP A AND B NORMAL CHILDREN
30 boys	3 to 10 inclusive	38.2 c.u.	28.1 c.u.	+10.1 c.u.
10 girls	3 to 10 inclusive	35.2 c.u.	28.5 c.u.	+ 6.7 c.u.

In summary, normal children in the vicinity of New York gave a mean acidity which, in the case of boys, fell between those figures given by Vanzant and those by Wright, and agreed well with the range used by Bray. In the case of girls, normal children had acid findings which were slightly higher than either the Vanzant or the Wright standards, and fell well within the range used by Bray. Even including the "possibly questionable" Group B, New York normal children agree closely enough with other standards of normal to eliminate the possibility that important differences in technic or geographic

TABLE V

SUMMARY OF DEVIATIONS FROM NORMAL IN FREE ACIDITY OF AUTHOR'S GROUP OF ALLERGIC CHILDREN

STANDARD OF NORMAL USED	AGE RANGE OF STANDARD	AVERAGE DEVIATION OF ALLERGIC CHILDREN FROM NORMAL	
		BOYS	GIRLS
Vanzant	3 to 19 yr. incl.	+15.5 c.u.	+11.7 c.u.
Wright	6 to 17 yr. incl.	+18.1 c.u.	+10.2 c.u.
Bray	Up to 13 yr. incl.	+12.9 c.u.	+ 7.7 c.u.
Author	3 to 10 yr. incl.	+10.1 c.u.	+ 6.7 c.u.

location were factors in the discrepancy found between findings in our allergic patients and those of other workers. When compared with Group A and B normal children, our allergic children had definitely increased free acidity.

Table V shows the units by which our allergic children deviated from normal when compared with standards by four different workers.

FACTORS WHICH MAY CONTRIBUTE TO THE FINDING OF LOW ACIDITY

Inasmuch as the foregoing gastric study failed to confirm the results of other workers who believe that allergic disease is associated with diminution of acidity, an attempt was made to discover what factors were involved in the discrepancy.

Preexistent Disease.—Since the existence of kidney dysfunction, cardiac decompensation, blood abnormalities other than mild secondary anemia, tuberculous infection, recent febrile or gastrointestinal disturbances (other than allergic), or rheumatic disease as brought out by Miller and Smith,[32] probably disturbs gastric secretion, patients with these complaints were eliminated from our series. All patients having even vague gastrointestinal complaints were given a roentgen ray examination, and any with organic abnormalities were dropped from the study. Two cases with possible gallbladder disease were not omitted, since Vanzant[26] and her coworkers have shown this does not alter gastric acidity.

Menstruation.—Care was used to avoid extraction at the time of the catamenia, inasmuch as it has been shown by Vanzant and Alvarez[33] that a fall in gastric acidity probably occurs at this time. Griffith and his coworkers[34] have shown that menstruation lowers decidedly the alveolar carbon dioxide tension; and Weissmann-Netter[35] found that a "compensated acidosis" was normal to the premenstrual period.

Mental State of the Patient.—Bennett and Ryle[36] felt convinced that the "idea of nausea" disturbed gastric secretion, and were able to eliminate this influence through hypnosis. Special attention was devoted to the prevention of fear and distress in our patients, both before and during extraction.

Drugs.—Alcohol, nicotine, adrenalin and ephedrine (in fact, all drugs) were interdicted for twelve hours previous to the extraction to prevent their possible influence upon the gastric secretory function.

Position of Tube in Stomach.—The tube was moved, during the course of the extraction, through a considerable area of the stomach, for there exists a striking variation in acid between the upper and lower portions of the stomach, the free acid averaging 12 units higher in the upper, according to Duthie.[37]

Method of Filtration of Contents.—In 23 of our early analyses, there was sufficient gastric juice to permit of titrating four different speci-

mens per patient. It was desirable to ascertain whether gastric contents should be titrated without filtration beforehand ("whole contents"), with filtration through several layers of hospital gauze, or with filtration through filter paper (Whatman No. 4). The content left in the filter paper, after filtration, was also examined for acidity in these 23 cases. Table VI gives the average in clinical units for the free and total acid in the 23 cases, using the different methods of treatment before titration. It will be seen that the highest free acid was found when the contents were filtered through gauze. When filter paper was used, findings in this filtrate were insignificantly lower in free acid than in the gauze filtrate. In a larger series the order would no doubt be reversed, since the paper filter more efficiently holds back food and mucus, both of which reduce free acidity by dilution and neutralization. The theoretical order of free acid readings would be as follows: highest in the filtrate from filter paper, next highest in the filtrate from the gauze filter, third in unfiltered contents, and lowest in the mucus and food left in the filter paper following filtration.

TABLE VI

VARIATION IN READINGS WITH DIFFERENT METHODS OF FILTRATION IN 23 CASES

GASTRIC CONTENTS	MEAN ACIDITY	DEVIATION FROM GAUZE FILTRATE
	Free Acid	
Filtered through gauze	35.7 c.u.	
Filtered through filter paper	33.9 c.u.	–1.8 c.u.
Unfiltered (whole)	31.4 c.u.	–4.2 c.u.
Filter paper content (after filtration)	30.6 c.u.	–5.1 c.u.
	Total Acid	
Filter paper content	55.9 c.u.	+3.5 c.u.
Unfiltered (whole)	54.5 c.u.	+2.1 c.u.
Filtered through gauze	52.4 c.u.	
Filtered through filter paper	47.5 c.u.	–4.9 c.u.

The findings for total acid, on the other hand, practically reverse the order for free acid, as would be logical; since the food and mucus neutralize, presumably, a portion of the free acid, converting it to total acid.

When 10 c.c. of juice are used for the titration, as was our routine, the difference between methods of filtration is less than 5 units—an unimportant figure in most determinations. When, however, smaller portions of juice are used (and some authors have used as little as 1 c.c.), the difference becomes magnified. It would seem advisable, at any rate, that the method used be the same by all workers. The gauze filter method was found to be quick and efficient in the present work, and all figures for acidities are based upon the gauze filtrate.

Titration End Point.—In selecting end points for titration, some authors have utilized the first color changes, while others depend upon

the maximal changes for reading points. To see how much variation this factor could introduce into the analyses, readings were taken for both end points in 62 of our cases. The average difference in reading between initial and maximal color change for the Töpfer's dye was 2.3 c.u. of free acid, and for the phenolphthalein dye 1.5 units of total acid. This deviation would be magnified if less than 10 c.c. of juice were used. The figures in this paper are all based upon points of initial color change, which favors low acidity slightly.

Saliva and Bile.—For obvious reasons, retching (which brings intestinal secretions into the stomach) and swallowing should be minimized during extraction. Bile was a rare finding in the gastric contents of the allergic subjects.

Mucus in the Gastric Contents.—Davies[38] holds that the "decompensating" stomach produces an increasing proportion of mucus as the acidity fails, and as decompensation progresses finally there is a gradual failure in the secretion of mucus. The first 20 cases of allergic individuals studied in our series definitely suggested a relationship between low acid and excessive mucus. Consequently, a record was kept on the proportion of mucus found in subsequent extractions. Among 120 cases, there were 31 cases having definite excess of mucus. Table VII shows that male allergic patients having excess mucus had a mean free acid 19.2 c.u. below normal and 9.5 c.u. lower than the male allergic patients as a whole; whereas allergic boys with inordinate gastric mucus fell 15.4 units below the allergic boys in general; allergic women with excess mucus fell 20.7 units below and girls 6.7 units below the allergic average for their respective groups. When these figures were weighted, it was found that the 31 patients pos-

TABLE VII

RELATION OF EXCESS GASTRIC MUCUS TO ACIDITY IN 31 ALLERGIC PATIENTS

CASES WITH EXCESSIVE MUCUS	N	DEVIATION OF MEAN ACID FROM VANZANT NORMAL		(M − m)*	N × M	N × m
	NO. OF CASES	M OF ALLERGIC CASES WITH EXCESS MUCUS	m OF ALLERGIC GROUP IN GENERAL			
Males over 20 years	7	−19.2 c.u.	− 9.7 c.u.	− 9.5 c.u.	−134.6	− 67.9
Males under 20 years	8	+ 0.17 c.u.	+15.5 c.u.	−15.4 c.u.	+ 1.3	+124.0
Females over 20 years	14	−17.6 c.u.	+ 3.1 c.u.	−20.7 c.u.	−246.6	+ 43.4
Females under 20 years	2	+ 5.0 c.u.	+11.7 c.u.	− 6.7 c.u.	+ 10.0	+ 23.4
	31				−369.9	+122.9

*Amount by which the mean free acid of allergic patients with excess mucus was lower than the acid of allergic patients in general.

$\frac{(N \times M) - (N \times m)}{N} = \frac{-36.99 - (+122.9)}{31} = -15.5$ c.u. The weighted mean lowering of acid in allergic patients having excess mucus as compared with acidity of allergic patients in general.

sessed less free acid than the allergic patients in general by the definite figure of 15.5 c.u. In addition to the 31 patients above, there were 2 patients with achlorhydria and excessive mucus.

Only 6 of the 31 patients had acidities higher than normal, the rest being below. Only 6 of the excessive mucus findings were in patients of less than fourteen years of age, so that the condition was 4 times as prevalent in adults as children.

It is possible that factors other than "gastric decompensation" may contribute, at least temporarily, to the presence of mucus in the gastric contents. One of these is the stomach tube. A very interesting experiment was conducted by Kahn and Stokes[39] to determine the effect of the passage of the stomach tube on titrable acidity of the gastric contents. They procured five patients, four of whom happened to be under nine years of age, who had gastric fistulas and patent esophagi. Their conclusions, after testing contents obtained through the fistulas and comparing with those obtained by stomach tube in the ordinary manner of extraction, were as follows. Passage of the tube and its presence in the stomach caused, in all but one patient, a definite lowering of the gastric acid. When the Ewald meal was used, the alteration due to the tube was less pronounced than in the case of fasting contents. As to the cause of the stomach tube effect, they made the comment that it was not apparently due to intestinal regurgitation. There was, they noted, definitely *more mucus present* when the stomach tube had been used.

Bray[13] stated in regard to gastric contents from his group of asthmatic children that "much mucus is usually present." Inasmuch as Fogelson[40] has shown that 1 gram of mucin neutralizes approximately 15 c.c. of tenth normal hydrochloric acid (in addition to the dilution effect), may this not be a factor in Bray's low findings?

Presence of an Asthmatic Attack During or Prior to the Test Period.—Of the 31 patients noted above as having excessive mucus in their contents, 10 (or approximately one-third) had asthma at the time of gastric extraction. This is suggestive of the idea that asthmatic attacks may, temporarily, lead to an increase of mucus and lowering of acidity. One boy of eleven years was subjected to gastric extraction twice. On the first occasion he had been free from asthmatic attacks for many weeks; on the second occasion, just a week later, he had had severe asthma (untreated) for eight hours up until the time he ate the Ewald meal. There were no other changed conditions discoverable, except the occurrence of the asthmatic state. The first analysis showed the boy to be 12 units above normal in free acid. The gastric juice obtained after the attack of asthma proved to be 6.5 units below normal—a drop of 18.5 units. There was a trace of mucus noted in the first specimen, whereas a great excess was found in the post-asthmatic sample.

Conditions of Underweight and Malnutrition.—The general opinion exists that debility contributes to gastric hypoacidity. With this in mind, weight and nutrition studies were made upon as many as possible (125 patients) of the author's allergic group. Those found underweight were then divided into two groups; i.e., those who were malnourished to physical inspection, and those who were not. As shown in Table VIII, 10 "technically underweight" allergic boys and girls, under fourteen years of age, proved to have free acid 5.8 c.u. lower than the allergic children as a whole. Nine additional children showed poor nutrition and poor tone on examination, as well as being underweight for their age and height; they averaged 3.3 units *above* the mean for allergic individuals of their age and sex. When both groups of underweight children were combined, they averaged only 1.5 units below allergic children in general.

TABLE VIII

FREE ACIDITY IN UNDERWEIGHT ALLERGIC CHILDREN

N CASES	U MEAN FREE ACID OF UNDERWEIGHT ALLERGIC CHILDREN	A MEAN FREE ACID OF ALLERGIC GROUP IN GENERAL	D (= U-A) DEVIATION OF UNDERWEIGHT ALLERGIC CHILDREN	N × U	N × A
		Technically Underweight			
2 girls	36.9 c.u.	36.0 c.u.	+0.9 c.u.	73.8	72.0
8 boys	35.7 c.u.	43.2 c.u.	−7.5 c.u.	285.5	345.6
		Underweight With Malnutrition			
2 girls	35.0 c.u.	36.0 c.u.	−1.0 c.u.	70.0	72.0
7 boys	47.7 c.u.	43.2 c.u.	+4.5 c.u.	334.2	302.4
				763.5	792.0

$\frac{N \times D \text{ (underweight girls)} + N \times D \text{ (underweight boys)}}{N} = \frac{-58.3}{10} = -5.8$ c.u. The weighted deviation in mean acid of "technically" underweight allergic boys and girls as compared with allergic children in general.

$\frac{N \times D \text{ (malnourished girls)} + N \times D \text{ (malnourished boys)}}{N} = \frac{+29.8}{9} = +3.3$ c.u. The weighted deviation in acidity of malnourished allergic children as compared with allergic children in general.

$\frac{(N \times U) - (N \times A)}{\text{total } N} = \frac{763.5 - 792}{19} = -1.5$ c.u. average deviation in acidity of all underweight allergic children (with and without malnutrition) as compared with allergic children in general.

Comparison of adults in the same manner gave the following results, shown in Table IX. Four "technically underweight" allergic adults averaged 13.7 units higher free acid than allergic adults in general. Ten who were underweight and "malnourished" averaged less than a half unit below the allergic mean. When the two groups were combined, the averaged weighted acidity was 3.8 units higher than allergic adults in general. When all 33 underweight allergic individ-

uals, with and without malnutrition, were combined and weighted, they averaged 0.7 c.u. of increased free acidity over allergic individuals in general.

Our allergic patients did not, therefore, show any consistent tendency toward a lowering of acidity in the presence of malnutrition. Malnutrition, however, is not necessarily synonymous with debility.

TABLE IX.

FREE ACIDITY IN UNDERWEIGHT ALLERGIC ADULTS

N CASES	U MEAN FREE ACID OF UNDERWEIGHT ALLERGIC PERSONS	A MEAN FREE ACID OF ALLERGIC GROUP IN GENERAL	D (= U-A) DEVIATION OF UNDERWEIGHT PERSONS FROM ALLERGIC PERSONS	N × U	N × A
		Technically Underweight			
1 woman	60.5 c.u.	35.9 c.u.	+24.6 c.u.	60.5	35.9
3 men	45.6 c.u.	35.2 c.u.	+10.4 c.u.	137.0	105.6
		Underweight With Malnutrition			
6 women	41.1 c.u.	35.9 c.u.	+ 5.2 c.u.	246.5	215.4
4 men	26.7 c.u.	35.2 c.u.	− 8.5 c.u.	107.1	140.8
				551.1	497.7

$\frac{N \times D \text{ (underweight women)} + N \times D \text{ (underweight men)}}{N} = +13.7$ c.u. weighted deviation in acidity of "technically" underweight allergic adults as compared with allergic adults in general.

$\frac{N \times D \text{ (malnourished women)} + N \times D \text{ (malnourished men)}}{N} = -0.28$ c.u. weighted deviation in acidity of "malnourished" allergic adults as compared with allergic adults in general.

$\frac{(N \times U) - (N \times A)}{\text{total } N} = \frac{551.1 - 497.7}{14} = +3.8$ c.u. average deviation in free acidity of all allergic underweight adults (with and without malnutrition) as compared with allergic adults in general.

Duration of Symptoms.—In order to ascertain the effect of *chronicity* upon gastric acidity, the date of onset of allergic symptoms was obtained in 122 of our allergic group. The "duration of allergic symptoms" in years was then plotted against the "deviation from normal free acidity" in c.u. Although a large number of cases would be required in order to determine this conclusively, our allergic patients did not evidence any relationship between chronicity of complaints and decrease in acidity.

ALLERGY AND THE ACID-BASE BALANCE

Considerable speculation has centered around the possibility that there exists in allergic patients a disturbance in the acid-base balance. For example, Tiefensee[20] found relative alkalosis during attacks of asthma, as did R. and S. Weissmann-Netter[41] just before attacks of migraine. Bray has suggested that perhaps the reason for deficient hydrochloric acid in allergic persons is that the blood has so little acid-forming material to spare. Previous references have been given for both sides

of this argument. The prevailing sentiment favors the theory that allergic states are associated with an alkalosis and improved by treatment counteracting this. Acid therapy by mouth has been given in the form of hydrochloric or nitrohydrochloric acid, acidifying salts or the ketogenic diet.

The ketogenic diet may produce the desired acidosis. On the other hand, it may produce practically no change in alkali reserve whatsoever, as found by Alexander,[24] and by Van Slyke and Cullen[42] who state that it is possible for man to excrete as much as 20 grams of ketones per liter of urine without lowering the blood bicarbonates (in other words, without producing acidosis). In three normal adults placed on a ketogenic diet by Apperly and Norris,[43] alkalemia was almost constantly present; this was perhaps the result of direct stimulation of the respiratory center by certain ketone derivatives in the blood, producing sufficient overventilation to outweigh any acidemia produced by the ketone acids. In view of these inconsistent effects on alkali reserve, the suggestion of McQuarrie[44] is timely—namely, that the benefit to epilepsy resulting from the ketogenic diet may be dependent upon changes in water balance. Myerson,[45] in treating vasomotor rhinitis, noted that the same beneficial results obtained when sodium chloride or sodium citrate was given instead of the acidifying regime, and thought that the favorable reaction was dependent upon a dehydration effect, common to all these treatments.

If acid therapy is helpful to allergic patients, the benefit may perhaps be dependent upon the diuresis that accompanies all forms of acid treatment.

The Body Buffer System.—Peters and Van Slyke[46] have published an authoritative description of the body buffer arrangement. All buffer systems consist of a mixture of weak acids plus their alkali salts or else a mixture of weak alkalies plus their acid salts. Carbonic acid with its alkali bicarbonate is a buffer, as also is the mixture of acid and alkali phosphate, and again the blood proteins plus their alkali salts. The plasma bicarbonate represents the excess of base present after all nonvolatile acids in the blood are neutralized, and expresses therefore the "alkali reserve" of the body. "Acidosis" exists when the alkali reserve has fallen below the normal level, a change which *precedes* an actual shift in hydrogen ion concentration.

If hydrochloric acid, a strong mineral acid, is added to the blood stream, the body changes it immediately as follows:

$$HCl + NaHCO_3 = NaCl + H_2CO_3$$

A neutral salt and weak acid have, therefore, replaced the strong mineral acid and bicarbonate. This reaction tends to lessen alkali reserve and, if pushed, even alters the hydrogen ion concentration of the blood.

Increased depth of breathing is the first clinical sign of acidosis and may be observed when the alkali reserve has fallen to half. The patient experiences no discomfort, and the condition may pass unnoticed by the physician. Later there is obvious air hunger. When the bicarbonates have fallen to half, the patient may develop nausea, malaise, headache, and later tachycardia. There is a great increase in kidney output of water, ammonia, fixed base and titrable acid. Haldane[47] reduced his own plasma bicarbonate to half by taking 15 to 20 grams of ammonium chloride daily (representing 102 to 136 c.c. of dilute hydrochloric acid). There was a fall of $pH_{0.2}$ in his blood stream, and he experienced dyspnea on exertion.

A simple index to the alkali reserve is to be found in the bicarbonate tolerance test.[46] When acidosis is present, the kidneys excrete urine more acid than blood; and in the presence of acidosis more than 0.5 gram of sodium bicarbonate per kilogram of body weight is required by mouth to turn the previously acid urine alkaline to litmus (bicarbonate tolerance test of Sellard). When this is negative, it is quite reliable and is an excellent rough measure of the alkali reserve.

This test was done on 25 of the allergic patients who were under acid treatment. Each patient was given 5 grams of sodium bicarbonate by mouth every two hours until the previously acid urine became alkaline. Almost always, one dose proved sufficient. Not one patient gave a positive Sellard, even those who had had 4 c.c. of dilute hydrochloric acid half an hour prior to the onset of the test.

From the results of these tests, and the failure of patients on acid therapy to develop clinical signs of acidosis, it was not expected that any marked changes in the acid-base balance would be found as the result of intensive acid therapy in the allergic group. Nevertheless, studies of the plasma carbon dioxide content were conducted on 9 patients.

The Alkali Reserve in Allergic Patients Under Intensive Hydrochloric Acid Therapy.—Of the 9 patients studied, 3 had true achlorhydria, one had hypochlorhydria, 4 had normal gastric acidity, and one had hyperacidity. They had each been on faithful and intensive acid therapy for weeks, the range being 8½ to 16 weeks and the average 13 weeks. The initial specimen taken for plasma carbon dioxide analysis was obtained before breakfast, the patient having taken no hydrochloric acid since the evening meal of the day before. Three of the group were tested again, this time not only being on the intensive acid regime but also having taken 4 c.c. of dilute hydrochloric acid within forty to fifty-five minutes of the time that blood was withdrawn. The purpose of this was to ascertain the immediate effect upon the acid-base equilibrium of mineral acid given by mouth. In

three patients a specimen of blood was also taken after abstinence from acid for two weeks.

All blood samples were withdrawn before breakfast in order to obviate the possibility of blood alterations due to the "alkaline tide" which follows ingestion, as Martin[48] has shown. Venous blood was taken according to the technic of Peters and Van Slyke,[46] without tourniquet and without contact of the blood with air. Prior to the withdrawal of the sample, thirty minutes of complete rest of the patient was required. Duplicate determinations were made on all specimens, and the analytical work was carried out by Mr. John Plazin at the laboratories of the Rockefeller Institute through the courtesy of Dr. D. D. Van Slyke.

The normal plasma carbon dioxide for venous blood is given by Peters and Van Slyke as ranging from 53.5 to 73.1 volumes per cent. Figures for patients on the hydrochloric acid regime, but without acid on the morning of the blood withdrawal, all fell within the normal range, with one borderline exception, as seen in Table X. Three patients, given 4 c.c. of dilute hydrochloric acid, U.S.P., forty to fifty-five minutes before the specimen was obtained, showed the following: One had a drop of 5.6 volumes per cent as compared with his first test, but both figures were well within normal limits. The other two patients each demonstrated a negligible rise. Bischoff and his coworkers[49] have recently shown that plasma bicarbonate values can vary normally by 3 millimols in prebreakfast blood; this is equivalent to 7.5 volumes per cent variation

TABLE X

EFFECT OF HYDROCHLORIC ACID THERAPY UPON PLASMA CARBON DIOXIDE OF ALLERGIC PATIENTS

SEX	AGE	GASTRIC ACIDITY	UNDER INTENSIVE HCl THERAPY			OFF HCl 2 WEEKS PLASMA CO_2
			TIME ON HCl	NO HCl A.M. OF TEST PLASMA CO_2	3 i HCl WITHIN HOUR OF TEST PLASMA CO_2	
F	33	achlor.	12 weeks	60.3 vol. %		59.8 vol. %
F	55	achlor.	14 weeks	68.1 vol. %		
M	58	achlor.	11 weeks	72.1 vol. %	64.8 vol. %	70.4 vol. %
F	42	normal	14 weeks	67.3 vol. %		
M	6	normal	8½ weeks	57.2 vol. %		
M	43	normal	15 weeks	.	64.1 vol. %	
F	22	normal	16 weeks	54.9 vol. %		
F	24	low	16 weeks 17 weeks	58.2 vol. % 52.9 vol. %	58.5 vol. %	55.8 vol. %
M	54	high	11 weeks	64.6 vol. %		

in plasma carbon dioxide. No patient showed a change of this magnitude under any of the circumstances of acid therapy surrounding the test, and all patients stayed within the normal range when they did show shifts.

The failure of patients to develop any clinical signs of acidosis as a result of acid treatment, the uniformly negative bicarbonate toler-

ance tests, and the normal alkali reserve findings all justify the conclusion that no significant change occurred in the acid-base balance of our patients as a result of intensive acid therapy. This is in accord with studies of Haldane.[47] In order to keep the blood hydrogen ion concentration and plasma bicarbonate below normal, he found that man must consume as much as 20 grams of ammonium chloride or 45 grams of $CaCl_2.6H_2O$ daily (equivalent to 136 c.c. and 150 c.c., respectively, of dilute hydrochloric acid). Haldane found that up to 500 c.c. of 0.116 N HCl (equivalent to 21 c.c. of dilute hydrochloric acid) could be taken by mouth within an eighty-minute period without a fall in alveolar carbon dioxide. Linder[50] experimented with normal adults, giving them 500 c.c. to 1,000 c.c. of tenth normal hydrochloric acid daily (equivalent to 18 c.c. and 36 c.c. dilute hydrochloric acid). He concluded that the normal kidney would readily deal with this amount of acid; whereas nephritic patients were liable to develop acidosis.

CLINICAL RESPONSE TO ACID THERAPY

A total of 75 patients submitted to intensive hydrochloric acid therapy for a period ranging up to six months, the average duration of treatment being three to four months. All patients were receiving, prior to and during the acid regime, indicated treatment in the allergy clinic, including pollen, dust, and vaccine therapy, elimination of etiologic foods and inhalants, and attention to foci of infection. Only patients who were at a clinical standstill or having increasing complaints were permitted to try the hydrochloric acid treatment. The ages ranged from four to sixty-five years. The diagnoses included the various forms of allergic disease studied in our gastric group.

TABLE XI

CLINICAL RESPONSE OF ALLERGIC PATIENTS TO INTENSIVE HYDROCHLORIC ACID THERAPY IN 75 CASES

IMPROVEMENT	MARKED (CASES)	MODERATE (CASES)	SLIGHT (CASES)	NONE (CASES)	"QUESTIONABLE" (CASES)
Initial	6 (8.0%)	11 (14.7%)	7 (9.3%)	18 (24.0%)	16 (21.3%)
Sustained	3 (4.0%)	7 (9.3%)	7 (9.3%)		
Total	9 (12.0%)	18 (24.0%)	14 (18.6%)	18 (24.0%)	16 (21.3%)

Reference to Table XI will reveal that there were 9 patients, or 12 per cent, who showed marked improvement with hydrochloric acid. In 6 of these the relief obtained was only temporary, lasting from one to three months (average, seven and one-half weeks). These 9 patients were under acid treatment for eleven to twenty weeks. Even the 3 who obtained sustained relief did not have complete alleviation of symptoms, slight asthma being experienced on a few occasions by each. These three were youthful asthmatic patients. One had gastric

hyperacidity, while two had normal acid secretions. The three children made unusual gains in weight and improved in general well-being under hydrochloric acid therapy. All three were being treated by dust injections, one having started this course five months, another three months and the third three weeks prior to the institution of the acid regime. As to the continuation of improvement after acid medication was stopped, one boy was seen a month later and was still free from asthma except for a slight wheeze on laughing. He had had fairly severe asthma for one week out of each month for some months preceding acid treatment and slight, infrequent asthma for six years before that. The second child was beginning to develop slight morning wheeze when seen one month after stopping hydrochloric acid. The third child developed asthma of unusual severity within a month following cessation of acid therapy. Hydrochloric acid has been recommenced but thus far (two weeks) has been of no avail.

Special mention should be given to one boy of twelve years who had severe giant urticaria. A few days of acid therapy enabled him to eat the etiologic foods with impunity, whereupon he abandoned the treatment after eight days and has continued free of urticaria for months since, despite the consumption of previously provocative foods. He stated that six days after hydrochloric acid treatment was instituted, he tried going without the acid for one day and had a prompt recurrence of hives, even without eating the harmful foods. This boy had been entirely free from urticaria for months at a time in the past, however; and it seems a bit naïve to attribute the present control of this capricious syndrome to eight days of acid therapy. The case was classified as one with marked improvement of "questionable" origin, and included in the last column of Table XI.

Of the patients showing less favorable response, there were 18 (24 per cent) who obtained moderate improvement. Seven of these 18 maintained the improvement during treatment, while 11 were given only "initial" help. There were 3 additional patients whose improvement may have been due to factors other than acid treatment, such as a change in residence or employment. They were placed in the group termed "questionable."

There were 14 patients (18.6 per cent) manifesting slight improvement under medication; and 12 others (16 per cent) whose slight benefits were questionable in origin. This brought the number of cases classified as showing "questionable" improvement up to a total of 16 (21.3 per cent).

Response of Different Types of Allergic Disease to Acid Therapy.—Eczema was diagnosed in 13 among the 138 allergic patients in the gastric group. The weighted acidity for the 13 was 7.2 c.u. below the weighted free acidity of allergic persons in general, being at the same

time, however, slightly above the Vanzant normal. Seven of these patients tried out the acid regime. Two manifested slight improvement during the several months of treatment, one became definitely exacerbated during five days of treatment, and four showed no change.

Urticaria.—There were 16 patients with hives or angioneurotic edema, 10 of whom were under twenty years of age. These patients were 1.2 c.u. increased in acid over the Vanzant normal. The weighted figure for the comparable group of allergic persons in general, however, was 9.3 c.u. above the Vanzant normal; so that the free acid of the urticarial patients was definitely lower (by 8.1 c.u.) than that of the allergic persons in general, but both were above normal. Of the 9 patients trying acid therapy, one became quickly worse, 2 showed no change, 2 showed slight improvement, 2 moderate betterment, and 2 marked improvement. Of the latter, one showed improvement for seven weeks, then had recurrences of her former urticaria despite faithful adherence to the acid regime. The second patient was the boy with giant urticaria who responded brilliantly to eight days of therapy as previously discussed.

Gastrointestinal Allergy.—Three boys and 2 women suffered this complaint. They had a weighted free acid 15.8 c.u. above the Vanzant normal, whereas the comparable group of allergic persons in general averaged 10.5 c.u. above the normal. Gastrointestinal allergy in this small group was associated, therefore, with an increase in free acid over normal and even over the allergic average. The one boy who tried hydrochloric acid was somewhat worse than when he omitted the treatment.

CONCLUSIONS

1. Studies of the gastric contents of 138 children and adults failed to reveal any correlation between allergy and a lowered gastric acidity; on the contrary, the mean free acid was higher in the allergic group than in normal.

2. Normal children in New York do not differ significantly in gastric acidity from children in other localities, and are definitely lower in acidity than are the allergic children.

3. In studying gastric acidity, the following factors may contribute to variation in results; viz., the method of filtration, the choice of color end points in titration, the presence of mucus in gastric contents, and the occurrence of an asthmatic attack near the time of gastric extraction.

4. Malnutrition in our allergic patients was not associated with diminution of gastric acidity.

5. The duration of allergic symptoms was not a factor which influenced gastric acidity in our patients.

6. Intensive hydrochloric acid therapy in allergic cases did not influence acid-base balance as revealed by the bicarbonate tolerance test and by studies of the plasma carbon dioxide content.

7. Allergic patients gave no impressive clinical response to intensive hydrochloric acid therapy.

The number of allergic patients who obtained definite and sustained relief is probably insignificant if one considers the possibilities of psychic influence and the law of chance.

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KAPOK*

Its Importance in Clinical Allergy

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KAPOK is a vegetable fiber which is found in the large seed pods of a tree which grows in the East Indies. The fiber and the pod of kapok look much like the fiber and pod of our common milkweed except that they are much larger and tougher. Kapok is used as an inexpensive filling for mattresses and pillows and for stuffing furniture. It is found in the houses of rich and poor alike; it is widely used. Most of the textbooks on allergy recommend kapok as a substitute for feathers. Our experience, however, is that in place of being less harmful than feathers, kapok is much more harmful. This statement perhaps can be modified by saying that when kapok is new, it often seems satisfactory at first but the difficulty is that after the material has been in use for a short time, the fibers become dry and brittle and soon break down into a fine dust which easily escapes through the outer covering of the pillow, mattress, or upholstery.

As will be shown, extracts of this old used kapok cause skin reactions in a large proportion of patients with asthma; and, when these patients are found to sleep on a kapok mattress or a kapok pillow or when they have furniture stuffed with kapok in their homes, the relief of asthma following removal of the offending substance is often striking. Our experience has been that kapok is a frequent cause of asthma. So far at least, this experience has not been matched by many students of allergy and, therefore, it seems desirable to present our own clinical findings. At the same time, kapok is a well-defined substance with the possibility of a definite structure, and, therefore, we have thought that a study of its chemical nature might throw light on the problem of allergy as a whole.

HISTORY

In 1922 Cooke[1] brought out his observations on the importance of house dust. He found that extracts of house dust gave positive skin tests in a great number of cases and he tried to correlate this observation with tests to a variety of other substances made at the same time, hoping to show that the positive reactions to dusts would run parallel to the tests with various common allergens. It is unfortunate that he did not include kapok among these other substances.

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As early as 1925, Storm van Leeuwen[2] observed that 50 per cent of his patients lost their asthma in the hospital within two days. He recognized that kapok was dusty, and he was suspicious of it in spite of the fact that the beds in the hospital contained kapok, and in spite of the fact that his skin tests to kapok extracts were negative. A paper by Frugoni and Ancona[3] gave him a new idea. These authors had observed that extracts made from feathers of different sources gave different tests, sometimes positive, sometimes negative, and so van Leeuwen undertook to test patients with extracts of kapok obtained from different sources. When allergic individuals were tested with extracts of pure kapok fresh from the factory, the results were almost always negative, whereas if the kapok was obtained from the beds of different asthmatic patients, more positive reactions were obtained. Van Leeuwen thought that the growth of molds was the cause of this phenomenon, and later he succeeded in growing various molds, especially *Aspergillis fumigatus,* from many samples of kapok. Furthermore, pure kapok which at first showed no reaction gave a positive reaction later when the material and its extract had been deliberately inoculated with fumigatus just as other extracts from kapok already infected with fumigatus reacted in many patients. It is obvious that van Leeuwen recognized the importance of kapok as a substrate for the growth of molds.

Feinberg in 1927[4] published a list of household objects as causes of hypersensitiveness and included kapok.

In 1929 Cohen[5] described his method of obtaining and extracting samples of autogenous dusts. He used a vacuum cleaner with new bags for each sample and made crude extracts in the clinic. He described the reactions of many patients with his material. Unfortunately, Cohen did not study kapok at that time.

In the same year, however, Brown[6] published a paper entitled "Cottonseed and Kapok Sensitization." He tested 232 patients with kapok protein and found 5 who gave a definitely positive reaction to it. Each of the 5 was sensitive to cottonseed at the same time. Most of his 232 patients were quite relieved of their symptoms after their mattresses and pillows had been changed.

Recently another paper has appeared by Cohen and others[7] which is very important for our subject and will be discussed presently.

EXPERIMENTAL

Old kapok with the fibers badly broken and the whole reduced to a soft dusty mass was obtained from patients' pillows and later from overhanging beams and shafting of a mattress factory. Extracts were made in Coca's fluid[8] and sterilized by Seitz filtration. Nine out of 10 patients with asthma gave a rather large skin reaction to the extract.

Separate samples of old kapok were obtained from an old pillow; each was adjusted to weigh exactly 5 grams and then was extracted with 200 c.c. each of various fluids—distilled water, Coca's fluid, decinormal sodium hydroxide, and 10 per cent sodium chloride. In addition, separate extracts in Coca's fluid were made of the kapok seed without fiber and of the ground-up hull of the kapok pod.* In each case, extraction was continued for twenty-four hours. The various extracts were tested by the scratch method on our patients. The results were entirely negative in 14 cases. Later, however, the intracutaneous method was used, employing full strength of the extracts, except that the sodium chloride extract was diluted ten times to make 1 per cent, and the sodium hydroxide extract was neutralized with hydrochloric acid. In this way 30 patients were tested. The water extract was positive in 26 patients; Coca's fluid in 26; sodium chloride in 20; and decinormal soda in 30. The seed extract, however, reacted in only 8 patients and the hull extract in only 5. During these tests, one patient developed a slight general reaction requiring adrenalin. A little later, this same woman was retested with the fiber extract and without the seed or bark extracts, but again she suffered a mild general reaction. Evidently, therefore, the active principle is contained in the fiber.

The next step was to study the relative intensity of the skin reactions by studying the responses to increasing dilutions of each extract. The intracutaneous method was used as before. Seven patients were studied. Some were so sensitive as to react to the 1:1,000 dilution of the original extract while others failed to react to anything more dilute than 1:10. In each case, however, the different extracts seemed to cause reactions of equal size in the different dilutions. Exceptions were the extracts of seed and hull which gave distinctly smaller tests than did the extracts of fiber. From these experiments, it was concluded that water, Coca's fluid, 10 per cent sodium chloride, and decinormal sodium hydroxide are equally effective in extracting the active principle.

Later in the work an observation of considerable practical value was made. The time needed for extraction is not long. Fifteen grams of old kapok were wet with 500 c.c. of buffered saline and stirred for only four minutes. Then the mass was squeezed and the fluid filtered through paper and a Seitz filter without delay. The same mass was then treated with another volume of 500 c.c. of buffered saline and filtered after a second four minutes. Then a twelve-minute extract was made, and finally the remainder was extracted in buffered saline for twenty-four hours, and filtered. All extracts were then taken to the clinic.

Ten patients were tested and all reacted to the four-minute extract. Only one patient reacted also to the eight- and twelve-minute extracts.

*All the raw materials were obtained through the courtesy of the Kapo Products Company of Cambridge, Mass.

A direct comparison of the four-minute and the standard twenty-four-hour extracts was made in four patients using the method of serial dilution. The reactions were practically identical. It may be concluded, therefore, that most if not all of the active material is removed at once. It is freely soluble. Very likely it is present on the surface of the fiber.

The studies to be described here, however, were all made with twenty-four-hour extracts.

PHYSICAL AND CHEMICAL PROPERTIES OF KAPOK DUST EXTRACT

Dialysis removes most of the active principle. Portions of the extract made with Coca's fluid were dialyzed in a No. 300 cellophane sac under toluene against four changes of extracting fluid for forty-eight hours. Only 4 out of 24 patients skin reactive to the undialyzed extract reacted to the dialyzed extract. The reactions elicited in each case were very small. From these observations it was concluded that dialysis had removed much of the active principle. Later the dialysis experiments were repeated with a No. 1200 in place of a No. 300 cellophane membrane, and again there was a great loss of the active substance. Presumably, its molecular size is small.

Boiling of the extract causes no change except in the case of the alkaline extract whose activity is thereby lost.

Charcoal absorbs all the active principle, as is frequently the case with other allergens. The fact suggests that extracts should be filtered only with care and not too often because presumably the particles in the filter itself will have the same adsorbing effect as charcoal.

Table I shows the chemical properties of the various extracts. Figures for the total nitrogen and for the nonprotein fractions are remarkably uniform. The Biuret reaction is negative throughout. Treatment with tannic acid and boiling with acetic acid give doubtful reactions. The presence of protein is distinctly doubtful. On the other hand, the reactions with Molisch reagent, Bial's reagent, and Tollen's reagent, indicate a sugar.

As already said, the results of skin tests show a remarkable uniformity in the activity of the various extracts; and it is, therefore, not surprising to find that chemical analysis gives uniform results, although the figures are a little higher for the decinormal sodium hydrate. All the figures are higher for this extract. Alcohol precipitation will be discussed later, but note here that, when the extract in alkali is precipitated by alcohol, the amount of nitrogen in the sediment is more than twice the amount obtained when the buffered saline extract is treated similarly. The difference can be explained by the greater ability of decinormal sodium hydrate to remove nitrogenous

matter (Table II). As will be described presently, however, the additional nitrogen in this case apparently bears little relation to the skin reacting principle.

The results shown in Table I also indicate that most of the nitrogen is nonprotein. Furthermore, in each extract the amount is very small. Evidently there is little if any vegetable protein present in kapok fibers. Protein chemical tests in like measure indicate a similar con-

TABLE I

NITROGEN CONTENT IN EXTRACTS AND QUALITATIVE TESTS
(MILLIGRAMS PER C.C.)

	WATER	BUFFERED SALINE	10% NaCl	N 10 NaOH
Total nitrogen	0.051	0.059	0.060	0.073
Nonprotein nitrogen	0.044	0.053	0.057	0.064
Protein nitrogen*	0.007	0.006	0.003	0.008
Alcohol precipitate weight	0.165	0.203	0.106	0.450
Total nitrogen in precipitate	0.002	0.004	0.002	0.005
Biuret	0	0	0	0
Tannic acid	±	±	+	+
Sulphosalicylic acid	±	±	+	+
Boiling with acetic acid	0	0	0	±
Molisch	++	++	++	++
Bial	+	+	+	+
Tollen	+	+	+	+

*By difference.

clusion. In making this statement it is appreciated that a large amount of polysaccharides in the extract could mask the Biuret reaction, but, on the other hand, the precipitation tests do indicate a small amount of protein.

The alcohol precipitates represent the material secured by treating each of the respective extracts with alcohol to a concentration of 80 per cent. No further appreciable amount was obtained by increasing the alcohol concentration to 95 per cent. Here again the low total nitrogen content of the precipitates favors the conclusion that most of the nitrogen present is nonprotein.

The dry weights of the different alcoholic precipitates show that each extracting fluid removes considerable soluble material. From the water extract, the precipitate weighs 0.165 mg. per c.c.; from the 10 per cent salt extract 0.106 mg. per c.c.; from the Coca's fluid 0.203 mg. per c.c.; and from the sodium hydrate 0.450 mg. per c.c. The last figure for the sodium hydrate extract goes with the other chemical tests to suggest that the material contains pentosans in some quantity.

The products of hydrolysis of the alcohol precipitate with 12 per cent hydrochloric acid gave positive test for carbohydrates including pentoses. The activity of the alcohol precipitates in eliciting skin reactions is discussed below.

Further studies of the chemical contents were made by analyzing the nitrogen distribution in a single 10 gram sample of old kapok, and

the results are compared with the skin test activity as shown by symbols to the right (Table II).

This experiment was so planned as to use one sample which was run through a number of chemical procedures in succession, each solution removing a greater or lesser proportion of the active principle. The total nitrogen is 0.766 per cent. Treatment with ether and alcohol removes only a very small quantity (0.011 per cent) of nitrogen, presumably in the form of lipids. The figure represents 1.49 per cent of the total nitrogen. So far as skin activity is concerned, this ether and alcohol extract is practically inert. Water alone removes 0.200 per cent of nitrogen, which represents 26.50 per cent of the total nitrogen. Most of the activity is in this water solution. When this water extract was precipitated with phosphotungstic acid, a slight precipitate was obtained, and in this the protein nitrogen (by difference) was 0.018 per cent which multiplied by 6.25 gives 0.113 per cent protein for the water fraction. It is interesting to note that the computed protein content of the aqueous extract of cotton secured by Knecht and Hall[9] is less than 0.1 per cent. Observe that the sodium hydrate fraction contains almost half as much nitrogen as the water fraction and yet is very questionable in its activity (Table II).

TABLE II

NITROGEN DISTRIBUTION AND TOTAL SOLIDS

FRACTION	NITROGEN	PER CENT TOTAL NITROGEN	SOLIDS	SKIN ACTIVITY
Whole (ash free)	0.766%	–	–	–
Ether 95% alcohol soluble	0.0113	1.49	0.98	0
Water soluble	0.2005*	26.50	3.21	++++
10% NaCl soluble	0.0204	2.69		+
75% alcohol soluble	0.0100	1.32	5.60	0
0.2% NaOH soluble	0.0918	12.10		±
Residue	0.4250	55.90	90.21	0
Total	0.7590	100.00	100.00	

*0.0181 per cent protein nitrogen.
Ash contents—2.8%

Total solids were determined by evaporation of 50 c.c. samples. Ether and alcohol remove 0.98 per cent of the solids. This figure is comparable to the finding of Cross and Bevan[10] in their studies of cellulose including kapok. They found that fats and waxes made up 0.05 to 0.18 per cent of the total substance. Water takes out a large quantity of solids, and the remainder comes out with the sodium hydrate later in the process.

Alcohol precipitation was the next step in the study. A water extract of old kapok made five days before was concentrated by suction and reduced pressure so that 100 c.c. was evaporated to 5.0 c.c. To this, 200 c.c. of absolute alcohol was added, the precipitate was centrifuged and redissolved in 100 c.c. of the original extracting fluid.

The filtrate was evaporated by suction down to 5 c.c., and then 95 c.c. of water was added to it. The two solutions, representing the original precipitate and filtrate, were sterilized by passage through Seitz filters and taken to the clinic. Twenty-five patients were tested, using the original kapok extract as a control; 17 patients reacted both to the original extract and to the alcoholic precipitate, while only 2 reacted to the alcoholic filtrate. These two, however, reacted to the saline control and can be neglected. The other 8 patients were negative to all tests. In no case did a patient react to the original kapok and not to the alcohol precipitate.

In another experiment, further attempts to purify kapok by alcohol precipitation were made. The precipitate in 75 per cent alcohol was redissolved in water and then reprecipitated successively with 80 per cent, 90 per cent, 95 per cent, and finally with absolute alcohol. In the course of this experiment it was noted that skin tests with samples of the successive fractions tended to become smaller as purification was continued. The first precipitate with the 75 per cent alcohol gave the largest skin reaction, while the last precipitate with absolute alcohol gave a smaller response.

When a solution of the alcoholic precipitate was treated with trichloracetic acid, no change was observed.

Ammonium sulphate precipitation was studied. Two samples, each of 200 c.c. of old kapok extracts, were treated, one with ammonium sulphate to 50 per cent and the other to full saturation. Both were placed in the refrigerator overnight, and then the precipitates were filtered and washed with 50 per cent and saturated ammonium sulphate respectively. Each precipitate was then dissolved in 100 c.c. of distilled water and reprecipitated as above. This same reprecipitation was carried out five times in all. The final solutions were dialyzed in a No. 1200 cellophane membrane and under toluene against running water until barium chloride no longer reacted, usually in about eight days. Fifty c.c. samples were then removed and passed through a Seitz filter. When these were tested in the clinic, the results were uniformly negative. We can say then that if the active principle brought down by the ammonium sulphate was a vegetable protein, at least it was not of large molecular size, and, if present, it was lost in the process of dialysis even with a No. 1200 cellophane membrane.

These studies as a whole show clearly that the skin activity of kapok is not a function either of the nitrogen factor or of the total solids. They indicate also that what little nitrogen is obtained is not protein in nature. The results with dialysis show that the active principle in kapok occurs in a small molecule.

About this time we realized that we had been working with old kapok obtained partly from pillows brought in by patients and partly from the old dust of the kapok factory. It seemed worth while to study

the chemistry of new kapok, since preliminary skin tests with its extract showed such marked differences from the old kapok. A supply of new kapok was, therefore, obtained. A fresh bale of kapok fiber recently received from Java was opened and a generous sample taken from the center. With extracts made of this new material, skin tests showed a marked difference. Many patients sensitive to the old kapok reacted little or scarcely at all to the new. When Coca's extracts were precipitated with alcohol to a concentration of 75 per cent and the precipitates were centrifuged, dried, and weighed, the relative weights were very interesting:

Kapok dust	0.307 mg. per c.c.
Old kapok	0.203 mg. per c.c.
New kapok	0.060 mg. per c.c.

When the precipitates were ashed in a crucible, the ash contents were negligible and, therefore, disregarded. Evidently, therefore, the amount of material to be extracted from new kapok is only a small fraction of what comes out of old used kapok.

To pursue this further, a comparative study was made of skin reactions to kapok of different origins and ages as follows:

1. Kapok dust from the beams and shafting of the factory—the age unknown.
2. Kapok from a mattress in use for five years.
3. Kapok from a freshly opened bale of raw material probably several months old (obtained through the courtesy of the Kapo Products Co.).
4. Kapok fiber from a freshly opened pod.

From each of these four samples, a similar extract was made (15 grams of material to 300 c.c. of buffered phosphate solution—Coca's fluid). Sixteen sensitive patients were tested with all four extracts by the intradermal method. All reacted to the dust; all reacted to the used kapok. Only 7, however, reacted to the fresh kapok, and only 1 reacted to the pod kapok and he reacted also to the saline control. Five normal nonallergic individuals were also tested. Two reacted and equally so to the dust and to the used kapok. One of them had been handling kapok for several months.

Obviously, a great change occurs when kapok is old and used. Age, however, is not the only factor. The pod kapok had come by freight from Java and after leaving the warehouse had been in the laboratory for five months before use. Its fibers were almost white, were resilient and lustrous. The new kapok had a similar age, but it was removed from the pod in Java, and in the laboratory was preserved only by wrapping in several sheets of paper. Its fibers were slightly yellow, less resilient, and had little luster. It had no dust. (Fig. 1.) Old kapok is yellow and has little if any luster; the fibers are brittle and form a dust readily.

Possibly, the new fibers are protected by a wax or resin. To test this, a small sample was soaked in ether for four hours, then dried, and extracted as usual. Skin tests, however, were negative, and the dry ether residue was also skin-test negative.

From the practical clinical point of view, these findings are of primary importance. They provide ample confirmation of the observations of Ancona and Frugoni, of van Leeuwen, and more recently of Cohen. Further study is in progress here. Meantime, a number of biologic studies of the extract of old kapok dust have been made.

Passive transfer experiments according to the Prausnitz-Küstner technic were made with old kapok extracts. The serums of two definitely sensitive patients were used to sensitize passively skin sites

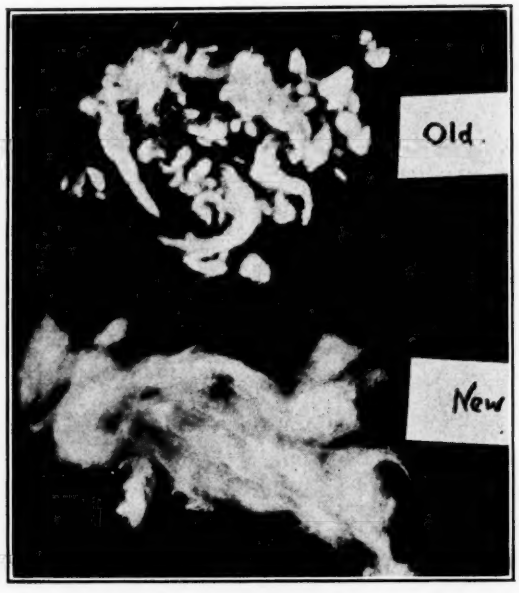

Fig. 1.—New and old kapok. Note the breakdown of the fibers with the formation of dust.

on 7 recipients. All these sites reacted well to the crude extracts as well as to the alcohol precipitates when tested in twenty-four hours. In another series of 38 kapok sensitive patients, blood was drawn and injected into an equal number of recipients known to be non-sensitive to kapok. Only 10 of the 38 serums were found able to transfer the kapok sensitiveness to normal individuals, that is, to have reagins. Nine of these 10 persons suffered from asthma. These results were somewhat disappointing in view of the large size of the original kapok tests.

To determine whether kapok extracts can sensitize guinea pigs, three sets of guinea pigs with 8 animals in each were obtained. One set received kapok dust extracted in water and concentrated by suction

to one-twentieth of its volume. The second received doses of the alcohol precipitate of the 1:1,000 water extract which was taken up in only 33 c.c. of saline. To all animals, injections were given intraperitoneally every other day in a series of four doses. Then after an interval of twenty-eight to thirty-eight days, a shocking dose of the corresponding material was given intravenously. Not one of the pigs in any one of the series showed any symptoms of anaphylactic shock. Van Leeuwen was unable to demonstrate sensitiveness to kapok by anaphylactic shock, but he showed that treated pigs developed respiratory symptoms when exposed to old kapok dust in a special chamber.

CONCLUSIONS

1. The clinical importance of kapok is described.

2. The similarity of extracts obtained with various fluids is striking both in the ability to produce skin tests and in the results of chemical analyses.

3. The active principle appears to be a substance of small molecular size, freely soluble in aqueous solution, precipitable by alcohol, giving in solution evidence of nonprotein nitrogen and possibly of a polysaccharide.

4. While kapok can produce positive skin tests in many patients, these tests are not often transferable by the Prausnitz-Küstner technic.

5. The extract does not produce anaphylaxis in guinea pigs.

6. The difference between new unused kapok and old used kapok is striking and of primary clinical importance, and this observation is quite in line with the observations of others on feathers and cotton.

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FUNGI FOUND IN PILLOWS, MATTRESSES, AND FURNITURE*

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IN THE preceding article, two of us have called attention to the clinical importance of kapok and particularly to the marked contrast between kapok which is new and unused and kapok which is old and used.

New kapok contains very little material which is soluble in watery solution, while old kapok provides an extract which contains appreciable amounts of nitrogen as well as of a carbohydrate-like substance. Extracts of new kapok rarely cause skin reactions in asthmatic patients, while extracts of old kapok react in a large majority of patients with asthma.

Why do the kapok fibers become so dry and brittle and break down so rapidly into a fine dust, and then, more important, what causes the marked change in the chemical properties? As a step toward the solution of this problem, it seemed desirable to make a study of the fungi found in the samples of the stuffing of various articles of bedding and furniture submitted by different patients.

The literature on mold allergy has been reviewed recently by S. M. Feinberg.[1] From his paper it is evident that most of the reports deal chiefly with the results of skin tests to molds and that little attention has been paid to mold cultures of various household articles. It seemed possible that if kapok had clinical effects different from cotton, hair, or feathers, the mold flora in kapok would be different from that in the other materials. Patients were requested to bring in samples (an envelope full) of various fillers and stuffings.

The method of study was simple. The material (kapok, cotton, hair, feathers, or wool) was placed in damp chambers and allowed to remain at room temperature for several weeks. The damp chambers were made in Kolle flasks in the following way: a layer of cotton was put in the flasks and smoothed out to cover completely the bottom of the flasks as they lay in a horizontal position. The cotton was then thoroughly wet with water and a thin layer of filter paper was made to cover the surface. The flasks were then closed with cotton plugs and sterilized in the autoclave for fifteen minutes at fifteen

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pounds' pressure, care being taken to keep them always in a horizontal position. After the flasks were sterilized and had cooled, bits of the test material (kapok, cotton, hair, or feathers) were put in the flasks on top of the wet layer of cotton and filter paper.

The moisture provided by such flasks was enough to make any spores and fragments of the various fungi contained in the samples germinate and produce growths along the filter paper and through the material itself. In two to three weeks the fungi were noticeable, and bits could be taken from the flasks for examination and identification. The various growths of fungi could also be transferred to agar slants, and in this way pure cultures could be obtained for further study.

A collection of fifty samples of various types of fillers was made, and each was put in a damp chamber, and a record of the fungi developing from each sample was made (Table I).

A study of this table shows that in this particular series, *Rhizopus* was the most common mold found. *Penicillium,* the common green bread mold, was a poor second. As for the several patients, there is no evidence that any one patient has a characteristic mold or combination of molds in his environment. There is, however, some suggestion that articles of furniture in the same room have a similar mold flora. Thus, for example, in Case 3, the two kapok pillows have the same molds. In Case 4, the kapok at college contains molds while the mattress and pillow at home are sterile. In Case 6, the kapok pillows have a slightly different flora from the cotton.

The question of whether kapok habitually contains a certain mold is clearly answered in the negative and similarly for the other materials. Table I gives no reason to indicate that any one mold or any one combination of molds is characteristic of a particular household article. *Aspergillus niger* was not often found, and most of the articles harboring it were of kapok, but in Case 8 the mattress contained this particular aspergillus. Other aspergilli "Aspergillus Species" were found four times in kapok and three times in other substances. Of the 50 samples in all, 27 were of kapok. It is interesting that not one of the kapok samples was entirely free of all molds. This leads to the next question.

Is kapok more moldy than other fillings? From the 27 kapok samples there developed a total of 55 different molds, an average of 2.04 molds from each sample. The other samples are 22 in number and contain together 38 different molds, or an average of 1.73 molds for each sample—a slightly smaller figure.

We can say then in brief that a variety of fungi is found in the samples of bedding and furniture submitted by various patients; that there is suggestive evidence that certain molds are characteristic of certain articles belonging to certain patients, but that no mold or

TABLE I

FUNGI CULTURED FROM VARIOUS TYPES OF FILLERS

PATIENT NO.	RESIDENCE	FURNITURE	STUFFING	RHIZOPUS NIGRICANS	CHAETOMIUM SP.	ASPERGILLUS NIGER	ASPERGILLUS SP.	PENICILLIUM SP.	MACROSPORUM SP.	ALTERNARIA SP.	STERILE
1	Fitchburg	P	K	+		+					
2	Harvard	P	K	+	+	+					
3	Smith	P	K	+	+						
	Smith	P	K	+	+						
4	Radcliffe	M (home)	Cot					+			
	Radcliffe	P (home)	Fea								+
	Radcliffe	M (college)	Hair								+
	Radcliffe	P (college)	K	+			+				
	Radcliffe	C (college)	K	+		+					
5	Radcliffe	P	K	+		+		+			
6	Greenfield	C	Cot	+	+						
	Greenfield	C	Cot	+	+						
	Greenfield	C	Cot	+	+			+			
	Greenfield	C	Hair	+	+		+	+			
	Greenfield	M	Hair				+				
	Greenfield	D P	K		+						
	Greenfield	D P	K	+		+					
	Greenfield	D	K	+		+		+			
7	Andover	P	K	+			+				
8	Haverhill	M	Cot	+		+		+			
	Haverhill	M	Cot	+							
9	Brookline	P	K	+	+						
	Brookline	M	Hair		+						
10	Boston	D	Cot	+				+	+		
	Boston	P	Fea								+
	Boston	Puff	Wool	+							
11	Andover	Puff	Wool	+				+		+	
	Andover	P	K				+	+			
	Andover	P	K	+							
	Andover	P	K	+	+						
	Andover	C	K		+			+			
12	Wakefield	P	K	+			+				
	Wakefield	C	K	+	+						
	Wakefield	P	Fea					+			
	Wakefield	M	Cot	+							
	Wakefield	C	Hair		+						
13	Allston	P	K		+						
	Allston	P	K	+				+			
	Allston	D P	K	+		+		+			
	Allston	M	Cot				+			+	
14	Atlantic	P	K	+	+						
	Atlantic	P	K		+			+			
	Atlantic	M	Hair		+						
15	Brighton	P	K	+		+		+			
	Brighton	P	K	+				+			
	Brighton	P	Wool					+			
	Brighton	D	K					+			
	Brighton	M	Hair		+						
	Brighton	M	Cot	+				+			
16	Cambridge (Factory)	Bag	K	+				+			
	Incidence of each mold			32	19	9	7	20	1	2	3

P=Pillow
M=Mattress
C=Chair

D=Davenport
K=Kapok
Fea=Feathers

Hair=Hair
Cot=Cotton
Wool=Wool

combination of molds is constantly found in all articles of a certain kind; but that, on the average, kapok seemed to harbor more molds than other kinds of furniture stuffing.

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THE INFLUENCE OF VARIOUS DRUGS UPON ALLERGIC REACTIONS*†

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DURING the course of investigations of patients with chronic allergic disorders, the question not infrequently arises concerning the possible influence upon skin reactions of drugs given for symptomatic relief, particularly such potent ones as adrenalin administered at frequent intervals. From a practical standpoint, it is important to know how soon after administration skin reactions are reliable or whether it is preferable to discontinue the use of all drugs during the testing period.

Although clinical experience of most allergists would seem to indicate that, with the possible exception of adrenalin, the inhibiting influence of most drugs upon skin reactions could probably be disregarded, nevertheless some doubt seems to exist as to the accuracy of tests done under these conditions, particularly in relation to weakly positive reactions.

Little assistance is derived from review of the literature. In Coca, Walzer and Thommen's book[1] the statement is made that "there has been little evidence to substantiate the statements which have been made from time to time as to other factors, which are said to influence skin tests, as for instance, the administration of iodides and bromides, the presence of tuberculosis, the season of the year," etc.; also, "the use of adrenalin or ephedrine on the day of testing should be avoided, if possible, as it may materially affect the size of the wheal, the secondary erythema and the pruritis associated with the reaction." In a recent summary, Bray[2] states that "the administration of drugs, especially adrenalin, ephedrine or acids, has a pronounced effect on lessening the reactivity of the skin to testing, whilst alkalies have a sensitizing action. It is advisable to stop all medication for at least twenty-four hours before performing the tests." The only reference upon which the statements concerning the adrenalin effect are apparently based is the publication by Lamson[3] in 1929, in which is is remarked that "epinephrine in the usual dose did not prevent the formation of definite positive skin reactions to pollen and histamine; in fact a few patients gave as large or larger reactions after epinephrine as before. In the majority, the reaction for one dilution was similar to that produced by the next higher dilution before the in-

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jection of epinephrine; thus the drugs decreased the reaction about as much as would result from a 1:10 dilution of the test substance. The secondary erythema was markedly decreased by the drug in most cases. With the use of a dose twice that previously used, a more marked interference with the genesis of the positive wheal was evident." No definite conclusions are, however, drawn from these experiments as to how soon after adrenalin administration skin tests can be performed with safety.

Because of the existing uncertainty concerning the exact influence of the various drugs upon allergic reactions, it seemed worth while to investigate this problem further in an attempt to provide more definite data. In the course of these experiments, additional facts of added clinical interest have been provided and are therefore included in the present report.

METHOD OF STUDY

Although the methods employed varied slightly in some of the experiments, the general plan of procedure was in most instances fairly uniform. This, in a general way, consisted in the preliminary testing of an allergic patient with the allergen (usually a pollen or dust extract) to which he gave a fairly marked skin reaction, then administering the drug and at frequent intervals thereafter retesting the individual to detect the effect upon the skin reactions. All the skin tests were carried out by the intracutaneous method, 0.02 c.c. being injected with a graduated tuberculin syringe. The reactions were always read exactly ten minutes after the introduction of the allergen.

The skin of the upper arm was employed as the testing area in all patients. In certain ones who were receiving injections of pollen extract, it was found that skin tests in these areas were either absent or greatly diminished. Because of such tendency to refractoriness, an effort was therefore made to avoid them.

The drugs employed were those most commonly used in the treatment of allergic conditions and included adrenalin, ephedrine, atropine sulphate, sodium iodide, and calcium gluconate, in addition to a few less commonly employed, as adrephine, asthmolysin, and aminophyllin. The latter, belonging to the caffeine-theobromine group, has been recently employed in our clinic for the relief of asthmatic attacks and for this reason was included in the present study. All the above mentioned drugs were usually administered in the experiments in the same manner as employed clinically, and, unless otherwise indicated, the maximum therapeutic dose was given. When the drugs were given orally, skin tests were, in some instances, made before the administration and as soon afterward as clinical effect was noted. When the drugs were given hypodermically, skin tests were made before, and coincident with, the administration, and continued at ten-minute intervals thereafter. In all instances the size of the wheal and erythema was traced and recorded, and wherever possible the effect upon the pruritis was noted.

EXPERIMENTAL

Controls.—In order to determine the character of the response to frequently repeated skin tests in patients who were not being given any drug, 10 allergic patients were skin tested at ten-minute intervals for one hour. Very slight variation in the skin reactions occurred in only one instance; the other nine patients showed no appreciable change. The tracings of these reactions were taken as a guide in estimating the extent of the reaction to the various drugs employed.

In the following experiments reactions which corresponded to the normal controls were classified as negative; those giving either questionable or slight reduction compared with the size of the control reaction or in which only one site showed slight reduction were considered doubtful; those showing a definite although slight reduction were considered slight; a moderate reduction was classified as moderate; and a marked reduction with almost complete or entire abolition of the zone of erythema as marked.

Adrenalin.—In the first portion of this experiment 8 patients were injected subcutaneously with 1 c.c. adrenalin chloride 1:1,000 dilution. Four of these were patients with late hay fever due to ragweed pollen and were first tested to ragweed extract (concentration 0.01 mg. N per c.c.). The other 4 patients, who had asthma, were tested with house dust extract. In 6 of the 8 patients the effect of the adrenalin upon the skin reactions occurred within the first ten-minute period; in the other two the effect did not occur until the second ten-minute period. In 6 of the 8 patients the injection of adrenalin produced a moderate or marked reduction in the size of the wheal and surrounding zone of erythema and either a distinct lessening or complete elimination of the pruritis. In the other two, only slight effect was noted. In all instances the most striking influence was upon the erythema—this effect was the earliest to appear and the last to return to the original size of the control. In all the patients complete return occurred within a period of thirty to fifty minutes after the injection.

In one patient the injection of adrenalin produced only a very slight reduction in the erythema with practically no effect upon the size of the wheal. It is of clinical interest that in this patient who was in the hospital ward because of severe chronic intractable asthma, the administration of adrenalin in the same dosage used in the experiment afforded practically no relief of the asthmatic attack.

In the second portion of the experiment an attempt was made to determine the effect of adrenalin in varying amounts upon different degrees of skin reaction. Accordingly, a series of patients were tested to three different dilutions of ragweed extract (0.0001 mg. N, 0.001 mg. N, and 0.1 N per c.c., respectively) and then given at different times 0.5 c.c., 1.0 c.c., and 1.5 c.c. of adrenalin and the effects upon skin tests noted in ten minutes, the time at which adrenalin effect was evident. Only one

reading was made after the injection. Ten patients were given 0.5 c.c. of the adrenalin; 8 tested to ragweed pollen extract and 2 to timothy pollen extract. Of these, 3 showed no effect at all, 4 showed very slight effect, and 3 showed moderate to marked effect. Little difference was observed with the various dilutions employed. The effect here as before was most evident upon the erythema. Five of these same patients were

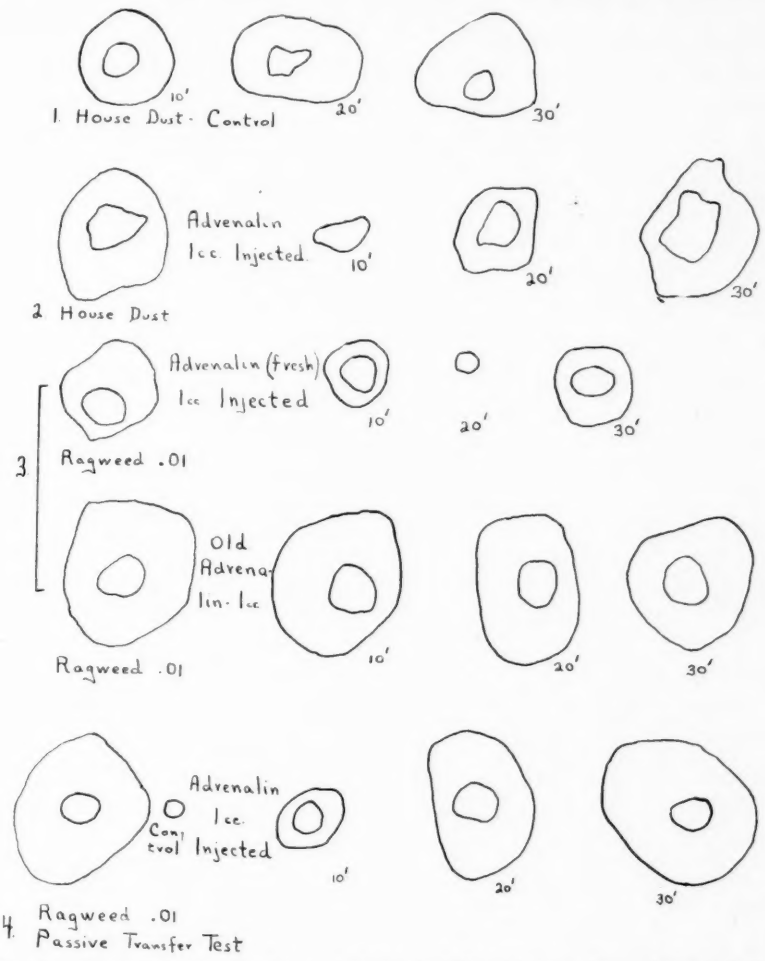

Fig. 1.—Representative tracings of characteristic skin reactions (wheal and surrounding zone of erythema) obtained before and after each administration of adrenalin.

given 1 c.c. of adrenalin. In practically all instances the reaction to the drug was only slightly greater than with 0.5 c.c., and in one was not at all influenced. These five patients were also given 1.5 c.c. adrenalin and here again very little additional effect was noted from the use of the larger amount.

In this group even though larger quantities of adrenalin were necessary in some patients to produce the full clinical effect, once this was

produced, the influence upon the skin reaction was the same as previously noted, irrespective of whether the skin test was slight or marked. Naturally, when only slight, the effect would be sufficient to obliterate it, and such a reaction might therefore be considered negative.

The third part of the experiment was devoted to a study of the effects of adrenalin which was old and apparently deteriorated. It was not possible to determine the exact age of the samples used, but in all instances it was over six months and had changed color. Four patients were tested, most of them being those who had previously been used in the first portion of the experiment and in whom the effect of the adrenalin had already been studied. In these the same amount of old adrenalin was used as the fresh.

The results obtained were not altogether unexpected. In three patients a distinct diminution in effect was noted when the old adrenalin was used, as contrasted with the fresh solutions. In the other patient the injection of the old adrenalin produced a fairly good effect but not so marked as that of the fresh product.

Ephedrine Sulphate.—In this experiment, five ragweed sensitive patients were tested with three dilutions of ragweed pollen extract (0.0001, 0.001, 0.01 mg. N), and ¾ grain of ephedrine sulphate in capsule form was then taken orally by each patient. Tests were repeated in twenty minutes, at which time the clinical effect was fully evident. In one patient there was no result whatsoever; in another a questionable effect was observed; in two it was slight; and in the fifth patient the effect was moderate. In a general way the results were somewhat similar to those with adrenalin but not nearly so marked. In all patients the full physiologic effect of ephedrine was noted.

Six other patients were given ¾ grain of the drug by mouth and tests done at ten-minute intervals. Four patients showed no effect at all in the course of one hour; in the other 2 patients it was only questionable. It is interesting by contrast that none of these patients exhibited any ephedrine effect after administration of the drug.

Four patients were given ¾ grain ephedrine subcutaneously. Two of these showed no effect; the other 2 were questionable. Here again practically no physiologic action was observed.

Adrephine.—This drug representing a combination of adrenalin and ephedrine (1:2,500 adrenalin and 3 per cent ephedrine per c.c.) was administered to 6 patients in doses of 1 c.c. subcutaneously. Practically all exhibited the same symptoms that occur after adrenalin. All showed some reduction in the size of the erythema and wheal, particularly the former. In 3 this was slight, in the other 3 it was quite marked. The result was in most instances similar to that of adrenalin except that there was more tendency for a delay in the return of the reaction to the original size.

Atropine Sulphate.—This experiment was similar to that with ephedrine. Six patients were given 1/75 gr. of atropine sulphate by mouth. As soon as the systemic action of the atropine was noted, which was usually at twenty minutes, the tests were repeated. In two other patients skin tests were done at ten-minute intervals. No effect was observed in any of the 8 patients tested.

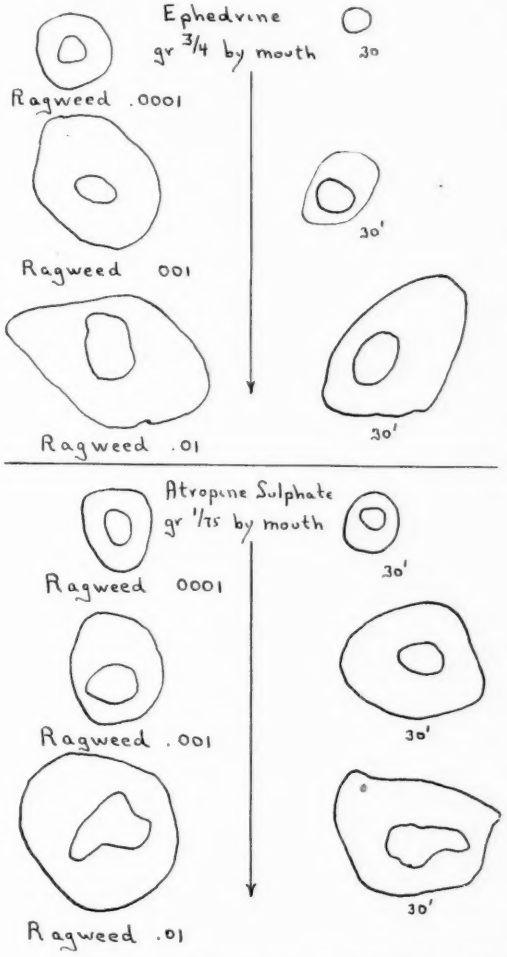

Fig. 2.—Representative tracings after ingestion of ephedrine and atropine.

Six patients were given 1/100 grain of atropine sulphate subcutaneously and skin tests done at ten-minute intervals. Of these, 5 showed no effect; in the sixth this was questionable. In practically all patients the physiologic effects of atropine were observed.

Calcium Gluconate.—Eight patients were given 10 c.c. of calcium gluconate intravenously. Skin tests were carried out with ragweed extract (0.01 mg. N) before the administration, coincident with it, and at

ten-minute intervals thereafter for one hour. In 6 patients no effect was noted upon either the wheal or the erythema; in one it was doubtful; and in another it was slight.

Sodium Iodide.—The same experiment was repeated with 10 c.c. sodium iodide instead of calcium gluconate. No effect was observed in 7 patients and a doubtful effect in one.

Aminophyllin.—Fourteen patients were tested in the manner used for the other drugs given intravenously. In 8 only one ampule (10 c.c.) was

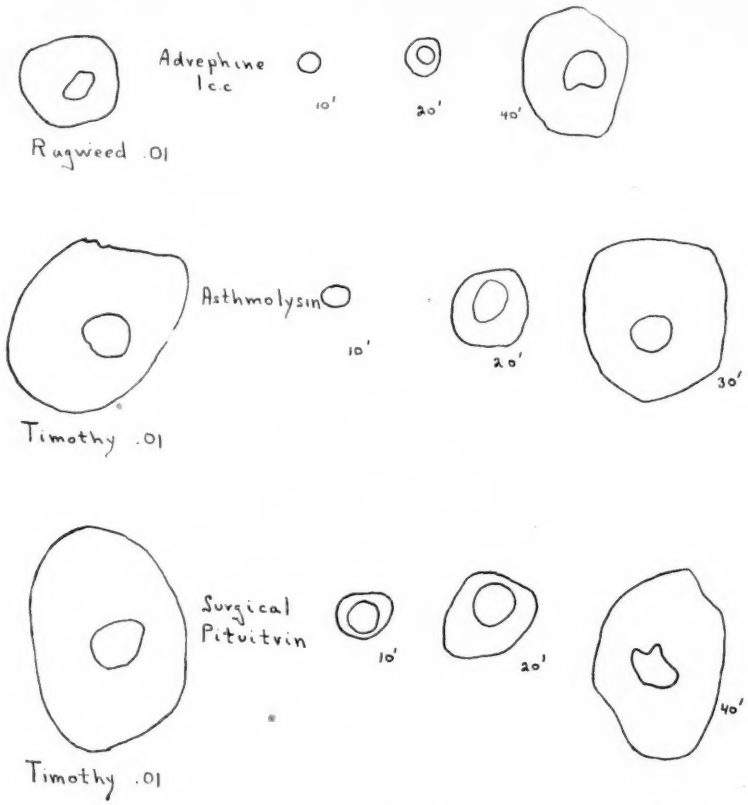

Fig. 3.—Tracings after subcutaneous injection of adrephine, asthmolysin, and pituitrin.

administered. Of these, 5 showed no effect, in 2 it was doubtful and, in the other, moderate.

In 6 patients, 2 ampules (20 c.c.) were administered. In 3 of these patients no effect was observed; in 1 it was questionable, and in the other 2, slight. The effect on the whole was similar to adrenalin although less marked, and not accompanied by abolition of the pruritis. In a few patients administration of the drug was accompanied by palpitation, flushing of the face and, in one instance, pain radiating down the left arm.

Asthmolysin.—This preparation, long advocated in the treatment of acute asthma, consists of a combination of adrenalin and pituitrin. It was tested upon 6 patients, all of whom had previously received adrenalin. The dose in all instances was 1 c.c. by subcutaneous injection.

The effect was quite similar to that of adrenalin but to slightly less marked degree in all instances. It was marked in 2, moderate in 1, slight in 2, and doubtful in 1.

In order to determine which portion of the asthmolysin accounted for the effect, 9 patients (some of whom included those previously injected

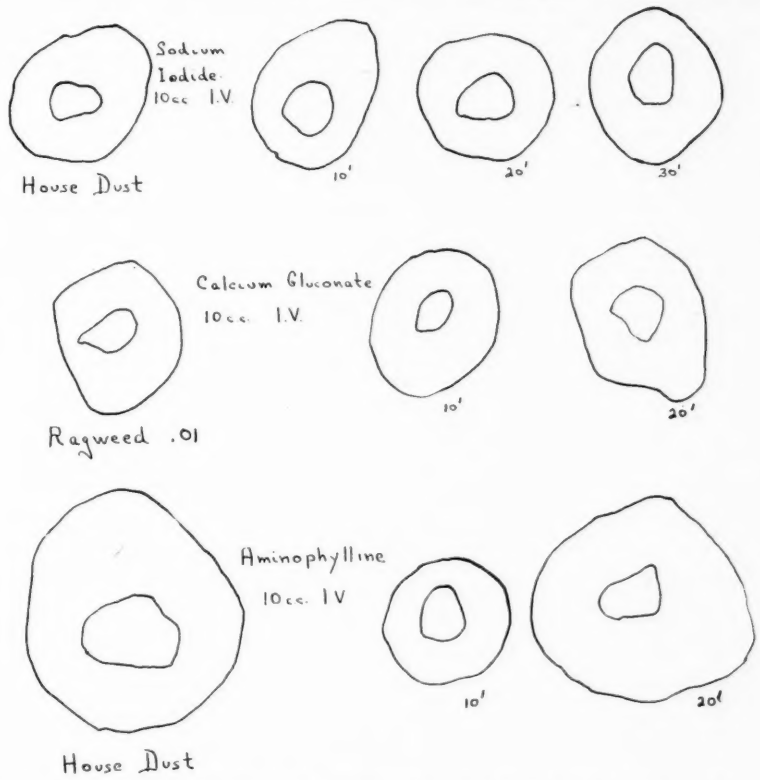

Fig. 4.—Tracings after intravenous administration of sodium iodide, calcium gluconate, and aminophyllin. (*I. V.*, intravenously.)

with asthmolysin) were given 1 ampule (1 c.c.) of surgical pituitrin. In 2 instances, no effect was obtained, in 2 it was doubtful, in 2 slight, in 2 moderate and in 1 marked, the reduction in the reaction occurring mostly in relation to the erythema. This effect was slightly less than that of asthmolysin in all but one patient—in whom it was more marked.

This effect from pituitrin is especially interesting in view of the prevalent opinion that the action of the asthmolysin is primarily due to the adrenalin content.

Passive Transfer.—From the above experiments it was evident that in allergic patients the effect of such potent drugs as adrenalin upon the

allergic wheal reaction was that of marked inhibition. Since the skin reaction is the result of an antigen-antibody reaction, it was of interest to determine, if possible, in what way the adrenalin inhibited the reaction—whether it was merely a reduction of the reaction as a whole or whether it acted by preventing the combination of antigen and antibody. Serum from a ragweed sensitive patient was injected into skin sites of 4 non-allergic patients. After forty-eight hours, one site was reinjected with ragweed extract, 1 c.c. of adrenalin was given and at ten-minute intervals the other sites were reinjected with ragweed extract. In one patient very little effect was observed, in one this was slight and in the other two moderate. The effect was particularly evident on the erythema and corresponded practically with that observed in previous experiments with adrenalin.

COMMENT

In reviewing the results of these experiments it is at once apparent that the effect produced by any of the drugs employed, occurred within a short time after its administration and was complete at the end of an hour, at which time the skin reaction in all instances had returned to its original size. It follows therefore that irrespective of the drug employed or its manner of administration, skin tests can be performed one hour later without fear of interference by the drug.

Of the group of drugs used, the most striking result occurred after adrenalin. This in many ways seemed to correspond closely with those observed after its clinical administration in the relief of acute allergic conditions such as asthma. Thus, the quick response (occurring within ten minutes after its administration), the fleeting action (lasting less than an hour), the abolition of the pruritis, the failure to produce any effect when used in average dosage on certain patients, the fact that a small amount may produce as marked an effect as a larger amount, and finally the fact that old and deteriorated adrenalin is not so active as the fresh drug: all these observations were made in our experiments, and the clinical and pharmacologic actions of adrenalin are thereby correlated.

The only other drugs which showed an effect upon the skin reaction similar to that of adrenalin were those which either were chemically related to it, as ephedrine, or contained adrenalin in combination with other drugs—adrephine and asthmolysin. Ephedrine, given either orally or hypodermically, showed comparatively slight effect. On the other hand, the action of adrephine was almost as marked as that of adrenalin alone, differing only in a slightly greater delay in the return of the skin reaction to the original size. This variance is probably accounted for by the contained ephedrine.

It was rather surprising, despite assumption to the contrary, to find that in certain patients reduction of the skin reaction did occur after

pituitrin injection. This suggests the possibility that pituitrin so used (asthmolysin) may enhance the action of adrenalin.

The absence of any effect after oral administration of atropine and the questionable effect after hypodermic injection are in accord with clinical observations as to its effect on the usual allergic reactions. The same thing may be said of sodium iodide and calcium gluconate.

The intravenous use of aminophyllin, on the other hand, was followed by slight or moderate reduction of the skin reaction in certain patients. The exact explanation of this is not clear. Our clinical experience with this drug is as yet too limited to warrant conclusions. In view of the observed effect upon the skin reaction, however, its further clinical trial would seem justified.

In all these experiments, the effect of the particular drug employed was determined upon a skin reaction which was in the process of formation; hence any observed effect related to the prevention of this whealing process. When used therapeutically, however, these drugs are usually employed in conditions in which the allergic reaction has already occurred. Although their action is probably the same in either instance, nevertheless it is important to determine, if possible, their effect upon a wheal already present. The results of such experiments will be reported in a subsequent communication. For the present, however, it might be said that these results are almost identical with those obtained in the experiments herein reported.

These added facts, therefore, serve to emphasize the striking manner in which the results of experimental study of the effects of various drugs upon skin reactions simulate clinical experience with their use. It suggests, also, the possibility of utilizing this method as a sort of therapeutic yardstick by which the activity and potency of new drugs advocated in the symptomatic treatment of allergic diseases may be measured.

CONCLUSIONS

1. Of the various drugs employed in the treatment of allergic conditions, the only ones which exhibited a decided inhibiting effect upon skin reactions were adrenalin or those drugs containing it in combination, as adrephine and asthmolysin.

2. Such inhibiting influence lasted less than one hour. Skin tests performed after this period can therefore be considered unaffected.

3. Close correlation was found to exist between the effect of the various drugs upon skin reactions and clinical experience with their use in the treatment of allergic conditions. Such correlation suggests the possibility of utilizing this method of study as a sort of therapeutic yardstick by which the efficacy of various drugs suggested for use in allergic conditions may be roughly determined.

4. The effect upon skin reactions of drugs such as pituitrin and aminophyllin suggests that further clinical trial with them is warranted.

On the other hand, the absence of such effect from either calcium gluconate or sodium iodide given intravenously is in accord with clinical experience and suggests that the use of these drugs for the relief of allergic conditions dependent upon an antigen-antibody mechanism lacks experimental justification.

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DISCUSSION

Dr. L. H. Criep.—I am very grateful to Dr. Tuft for his simple and direct presentation, for it has definite and practical applications by inference. In the first place, I know that many of us have been troubled with the question as to whether or not medication interferes with skin testing. The patient may be taking ephedrine right along, and we sometimes wonder whether or not this interferes. The paper answers this question for us.

In the second place, both Dr. Tuft's paper and the paper by Dr. Walzer may offer some information with regard to the time of absorption and the duration of effect of certain drugs, as well as a comparison of the absorption time when drugs are given subcutaneously, by mouth, or in other ways. This is a question of practical importance in every therapeutic procedure.

Finally, this work might lead to some help with regard to a proper evaluation of the effect of certain drugs in the treatment of allergic conditions.

I am interested in the fact that Dr. Tuft indicates that the effect of adrenalin as far as its inhibitory action on the skin is concerned, disappears in forty minutes. Dr. Walzer's paper indicated that antigenic substances remain in circulation from five to fifty hours. May there be a difference in the time of absorption and excretion between nonantigenic substances such as drugs on the one hand and antigenic substances on the other?

Dr. Swineford.—Dr. Tuft has saved me some trouble. I am in the midst of just such an experiment. I have so far tested only four patients.

We started by producing in the test patient 4 plus, 3 plus, 2 plus, and 1 plus scratch skin reactions. We then gave adrenalin ♏ xv and took the blood pressure and the pulse rate every five minutes. In these four patients the results were completely uniform. The 4 plus reactions were reduced considerably to perhaps 1 plus or 2 plus. The 3 plus and 2 plus reactions were significantly reduced but were not eradicated. The 1 plus reactions became doubtful or negative in each patient. The effect of adrenalin on the skin test was not manifest until the blood pressure was raised a few points or until the pulse had been raised a few points. The time element was as Dr. Tuft has reported. The tests were repeated every fifteen minutes. In forty-five minutes after the administration of

adrenalin the skin tests had begun to get back their original titers, and in sixty minutes there was no demonstrable effect of the adrenalin.

There is another aspect to this problem which I anticipate pursuing. Some years ago the effect of enhancement of sensitization in guinea pigs by the administration of quinine was reported. In other words, guinea pigs which had been sensitized to horse serum and in which the titer of the shocking dose had been determined were made significantly more sensitive by the administration of quinine. That brings up the question of whether some drug like quinine, administered before a skin test, could make a doubtful skin test significantly positive.

DR. EFRON.—I was very glad to hear that aminophyllin was included in this study. We have been using it in cases of asthma, that do not yield to adrenalin, purely for relief. In a surprising number, we found we were able to stop attacks of great severity by the intravenous administration of aminophyllin. Van Leeuwen first suggested the use of drugs of this series three years ago. We use the 10 c.c. ampule or the 2 c.c. ampule. For the person with large veins, we use the 10 c.c. ampule. A word of caution is necessary. A single drop under the skin may require novocaine to stop the excruciating pain that often occurs; the drug also has a tendency to sclerose veins. The use of aminophyllin as a preventative, however, regardless of the amount of tablets we had given, played no rôle in the cessation of the asthma.

DR. L. TUFT.—In answer to Dr. Swineford, we carried out the same procedure on patients who had slight, moderate, or marked reactions, and our results as shown in the slides are quite corroborative of his findings.

In regard to aminophyllin, we have used it in the past year intravenously and by mouth. It also seems to have some beneficial effect when given by mouth in combination with theobromine and caffeine. We have no explanation for this action, but certain patients do seem to obtain relief in acute attacks from the administration of the three drugs above mentioned.

THE IMMUNOLOGIC ASPECT OF TOBACCO IN THROMBOANGIITIS OBLITERANS AND CORONARY ARTERY DISEASE*

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AMONG the numerous etiologic factors of thromboangiitis obliterans suggested since 1908, when Buerger first described that clinical and pathologic entity, tobacco has been recognized as one of the important excitants. This was ascribed to the toxic effect of its nicotine content on the sympathetic ganglia.

These pharmacologic effects have been described by Johnson,[1] Salisclus-cheff and Tschernagradoff,[2] and Grollman.[3] Maddoch and Coller[4] noted in young healthy smokers a lowering of the surface temperature and an increase in pulse rate and of blood pressure. These changes were most marked in the tips of fingers and toes, lasting as long as one-half hour, usually of greater duration in the toes. Similar results were obtained in cases of thromboangiitis obliterans. This, in their opinion, was due to vasoconstriction of the peripheral arteries, arterioles, capillaries, and venules. They considered the effects to be proportionate to the amount of smoke inhaled. Barker,[5] while confirming the above observations, thought that the effects of tobacco depend upon individual sensitiveness and not upon the amount of tobacco used.

Wright and Moffet[6] have recently been able to produce a drop in surface temperature as great as 15.5° F., with an average drop in a series of normal individuals of 5.3° F. during the process of smoking. They also observed a slowing of the capillary circulation in the nail folds during the smoking of cigarets. In their opinion the length of time a subject has been a smoker and the number of cigarets habitually smoked had no relation to the degree of temperature drop. Lampson[7] was able to demonstrate experimentally that patients with thromboangiitis obliterans responded to tobacco in the same manner as did normal individuals.

The effects of tobacco on the coronary vessels have been mentioned as far back as 1858. Moschovitz,[8] however, was the first to report four cases of what he called "tobacco-angina-pectoris." White and Sharber,[9] although not impressed with tobacco as a cause of angina, state that some individuals may be more sensitive to tobacco than others.

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The first attempt to approach these two conditions from the immunologic aspect was made by Harkavy.[10-13] He studied 87 cases of thromboangiitis obliterans and 36 cases of coronary disease. In the first group he obtained 87 per cent positive skin reactions to tobacco, with 15 successful passive transfers. In the latter, 36 per cent gave positive skin tests with four passive transfers. As controls he used 262 nonvascular cases. He obtained positive tests in 16 per cent of them. Sulzberger[14] confirmed Harkavy's observations so far as positive skin tests were concerned. He was unable, however, to obtain any positive passive transfer. He felt that sensitization of the vascular system to tobacco played an important rôle, but he did not consider it an atopic condition (local sensitization).

We became interested in this problem about one and one-half years ago. Our plan was to use the various brands of tobacco mentioned by Harkavy, who was kind enough to furnish us with a quantity of his extracts. To these we added extracts of various brands of frequently used cigarets and cigars, as well as the Arlington extracts used by Sulzberger. We also added to the list Coca's solution, exposed to smoke, and an extract of cigaret paper. As controls, we employed ragweed, timothy, house dust, and feather extracts. Our extracts were made according to the method of Coca. Testing was done by the intracutaneous route, and the quantity injected varied from 0.01 c.c. to 0.02 c.c.

We used various groups of cases for control purposes and directed our attention to the following: (1) thromboangiitis obliterans, (2) coronary thrombosis, (3) normal nonsmokers, (4) normal smokers, (5) allergic smokers, (6) allergic nonsmokers.

Group 1 consisted of 31 proved cases of thromboangiitis obliterans. Only one was allergic, but five gave positive family histories of allergy. Eighteen were under fifty years of age, and thirteen were over fifty years. Twenty-eight were smokers, and three were nonsmokers. The duration of the disease varied from six months to twenty-one years. Five reacted mildly to tobacco with skin tests. One reacted to only one brand. He was a smoker of that brand. Almost all reacted to one or more of the other allergens. There was 16 per cent positive skin reactions to tobacco. No reagins were demonstrated by passive transfer.

Group 2. Of 23 cases of proved coronary artery disease only one was definitely allergic, and one gave a family history of allergy. Three reacted to tobacco, and six to other inhalants. Two gave slight reactions, and the third gave a moderate reaction. The percentage of positive skin tests to tobacco was 13. No reagins were demonstrated.

Of Group 3 consisting of 52 normal nonsmokers, 11 reacted slightly to tobacco, nine to house dust and feathers, and two to timothy extract. Passive transfers were negative. There was 21 per cent positive skin reactions to tobacco.

In Group 4, three out of 40 normal smokers had a family history of allergy. Seven reacted slightly to tobacco, two to house dust, and one to timothy. Passive transfer tests were negative. The percentage of skin reactions to tobacco was 17.

Group 5 contained 17 allergic smokers. The allergic conditions for which they were treated comprised bronchial asthma, seasonal hay fever, and atopic vasomotor rhinitis. Tobacco played no part in their clinical manifestations, a fact which applies also to the following group of allergic nonsmokers. Eight reacted (mild to moderate degree) to tobacco, and all reacted to the remaining allergens. There was 47 per cent positive reactions to tobacco.

Group 6. Of 24 allergic nonsmokers, six reacted to tobacco slightly, and all reacted moderately to the other allergens. One positive passive transfer was obtained. There was 25 per cent reactions to tobacco, an average of 34 per cent in the 41 allergic persons. We noticed no difference in the reactions to individual brands of tobacco or of cigarets except the one case mentioned above.

Our studies were completed a long time ago, but we hesitated to report our findings because we had but 9 cases of thromboangiitis obliterans. Through the courtesy of Dr. Steel, of the vascular clinic of the Temple University Hospital, we were recently able to study 22 additional patients in his clinic.

While we have seen many cases of peripheral vascular diseases, many of them belonged to the group of obliterating arteriosclerosis. They frequently resemble thromboangiitis obliterans, and the two are often difficult to differentiate. We felt that only proved cases of the latter should be included in this report.

DISCUSSION

Although it is theoretically plausible that hypersensitiveness of the vascular system to tobacco is the mechanism in thromboangiitis obliterans and coronary artery disease, our studies, we believe, do not justify this contention. We have frequently noticed direct relationship between vascular crises and smoking, whether symptoms occurred in the lower extremities or in the coronary system. Three of our patients with thromboangiitis obliterans, and four with coronary disease volunteered the information that smoking initiated pain. We were able to demonstrate definite electrocardiographic changes during the process of smoking in a few of our patients. This, however, will form the subject of a further report. The explanation of symptoms in the light of our observations must rest on a pharmacologic basis only, namely, that tobacco or its derivatives react directly on the sympathetic nervous system causing a vasoconstriction which is manifested as an increase in blood pressure and pulse rate with a lowering of the surface temperature of the

skin. This has been well proved by Wright and Moffet.[6] Nicotine may not be the element at fault, and there are still many toxic substances in tobacco which cannot be definitely eliminated.

While our series is relatively small, the results are uniform. The only group in which the percentage of positive skin tests was comparatively high (34) was the allergic. It is known, however, that many nonspecific reactions are frequently obtained in such individuals. Of 63 unselected asthmatic children from the ages of three to twelve years whom Chobot[15] tested to various tobacco extracts, only 6 gave negative skin tests. Tobacco apparently was not an etiologic factor in their asthma.

The incidence of cases in which tobacco is a proved atopen is not very great. According to Brown[16] tobacco accounts for 1 per cent in the nosology of his asthmatic patients, while in our experience it amounts to less than 1 per cent. The failure to demonstrate reagins for tobacco on passive transfer tests in all patients except one, who reacted to tobacco, also argues against its significance in allergy. If, however, one should remove this objection on the basis that occasionally atopic conditions occur in the absence of reagins, why should there be so few cases of thromboangiitis obliterans and coronary disease among allergic individuals? Of the hundreds of allergic patients we have studied, we do not recollect any with thromboangiitis, and no greater proportion of coronary disease than one ordinarily meets among the nonallergic persons about the fifth decade of life.

It is interesting to note that there is no essential difference in skin reactivity to tobacco between the normal smokers and nonsmokers.

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Special Reports

HYPERSENSITIVENESS TO ARSENIC

Dermatitis From Liquid Arvon*

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THE untoward effects from the injection, ingestion, or external contact with arsenic and its compounds have long been known. The details of its various allergic manifestations, however, are not so well known because such reactions are rarely recognized as allergic, very often are not traceable, and even when discovered are usually not reported. As the sources of arsenic are widespread in various foodstuffs, ingestion of it is surprisingly common. Its rôle as a probable factor in the genesis of certain skin disorders merits greater attention than it has hitherto been accorded.

A study by Throne, Van Dyck and their collaborators[1] resulted in the conclusion that arsenic is a significant etiologic agent in about 30 per cent of the cases diagnosed clinically as eczema. This was confirmed in an investigation of 105 infants and young children by these same authors.[2]

Cooke[3] gave proof of the allergic nature of certain drug reactions generally. Arsenic hypersensitiveness in the form of post-arsphenamine dermatitis has been intensively studied and exhaustively reported in the literature.

In a series of experiments by Sulzberger,[4] and by Sulzberger and Mayer,[5] the skin of guinea pigs was sensitized to neoarsphenamine by the intradermal injection of the drug. Jui-Wu Mu[6] confirmed their work on Japanese rabbits. Stokes and Kulchar[7] presented proof of the allergic nature of the reaction to arsenic and established the fact that a true specific (allergic) sensitivity exists. Clinical evidence was collected by Nathan and Munk[8] and by Frei[9] to show that an allergic susceptibility to arsphenamine may be induced in man by intradermal deposition of the drug. After an interval following such injection, a sudden dermatitis occurred upon intravenous injection. In the study of patch tests, Kaplan and Moreinis[10] and Schoch[11] verified these observations. Nathan and Grundmann[12] found that this induced allergy was limited to the salvarsans, the arsenic compounds of the aromatic series.

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Arsenic also merits serious attention because of the untoward effects resulting from external contact with different forms of the drug. Reports dealing with this phase of susceptibility are meager, only a few being available in the literature. Klauder[13] observed a case in which asthma and eczematoid dermatitis had persisted for eight months. It was found that the patient, a physician, developed these respiratory and cutaneous symptoms whenever he administered neoarsphenamine or came in contact with the drug. A case of erythema multiforme bullosum was described by MacDonald,[14] in which the eruption resulted nine days after treatment of a carious tooth by an application of an arsenical preparation for the purpose of devitalizing the nerve supply. Two days after the application the patient noticed that her hands and feet were slightly swollen and itched. Five days later she consulted a physician, who prescribed Fowler's solution. After the fourth dose the bullous eruption suddenly appeared. Here we have an example of arsenic allergy from external application and from internal medication. Vuletic[15] described a type of hypersensitivity to arsphenamine that developed in him and his assistant as the result of daily contact of the fingers with arsphenamine solutions and from inhalation of the solutions when they administered antisyphilitic treatment to numerous patients in Bosnia. Neither he nor his assistant had ingested arsphenamine in any form. The disturbance became manifest at first as a mild dermatitis of the fingers, but later deep fissures and structural changes of the skin developed. Typical attacks of asthma occurred only when they worked at one particular station, and it was found that the air of the room that they used contained dust in addition to arsphenamine vapors. The assistant developed, in this epicutaneous manner, a universal arsphenamine urticaria, Quinke's edema, and acute arsenic intoxication.

Our case, of which a detailed report is here given, shows an intolerance to arsenic from external application. Commercially, the medicament is known as Liquid Arvon and is advertised widely for its effectiveness in removing dandruff when applied to the scalp. The idiosyncrasy to this hair tonic and dandruff remover manifested itself as a generalized dermatitis. We determined that the intolerance was due to the sensitivity of the patient to the arsenic in the hair tonic and not to any other substance contained in it. In our opinion, the occurrence assumes a rôle of importance from the point of view of public health.

Specific reactions to the use of Liquid Arvon have been reported to the Bureau of Investigation of the American Medical Association.[16] These reports were compiled at the Bureau in response to inquiries for the chemical composition of this lotion by physicians who have

observed dermatitis following its use (and by one attorney who was retained by a client suffering extensive dermatitis of the scalp following its application). The chemical laboratory of the American Medical Association analyzed the preparation and determined the presence of (1) salicylic acid, (2) resorcin, and (3) potassium arsenate equivalent to approximately 17 c.c. of solution of the compound U.S.P. in 100 c.c. of Liquid Arvon.

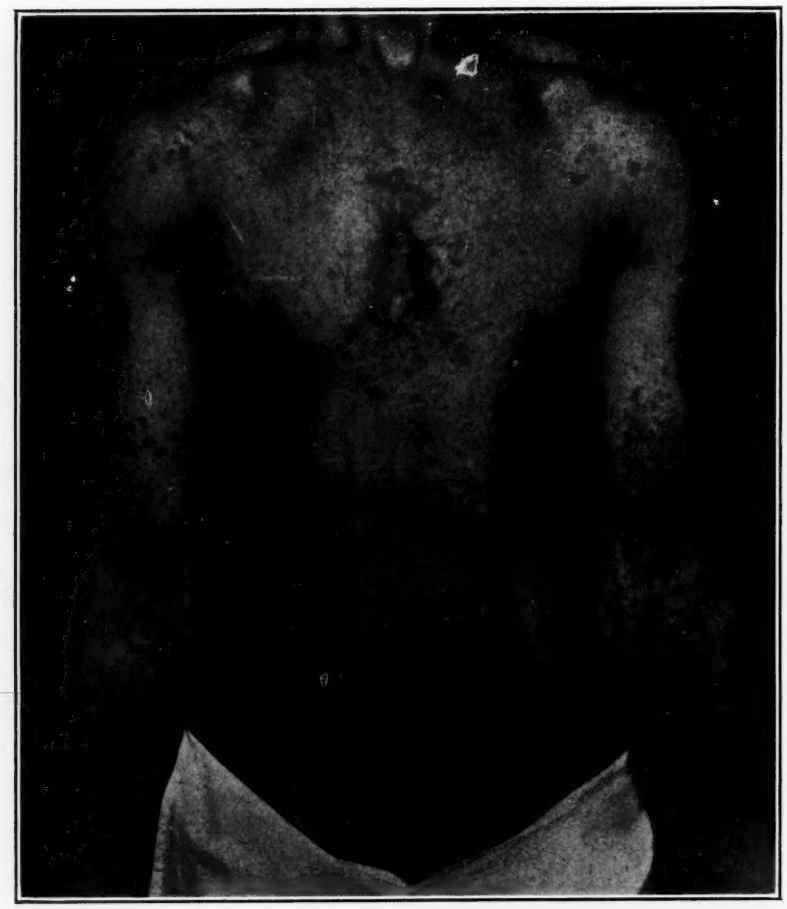

Fig. 1.—Arsenic dermatitis from the application of Liquid Arvon.

In the study of our patient, making use of this information, we eliminated all ingredients other than arsenic as an irritant. Arsenic was thus proved to be the etiologic factor because of the positive patch test obtained. Normal individuals tested with arsenic and Liquid Arvon by patch, proved negative. Passive transfer on normal individuals, by making use of the serum from the sensitive patient, also failed to give positive reactions.

REPORT OF CASE

W. W., a young man aged thirty-one years, applied for treatment on March 6, 1934, because of a generalized dermatitis resulting from the application of the hair tonic Liquid Arvon to his scalp. The onset was gradual and assumed its severe nature only after the third application.

Fig. 2.—Arsenic dermatitis generalized over the entire body.

After the first application of hair tonic on Feb. 13, 1934, nothing more than a slight itching was noticed. After the second application twenty-four hours later, the itching increased and was accompanied by redness and peeling of the skin on the forehead. After the third application, two days later, (1) there was a sensation of "burned skin" with marked itching over the entire scalp, (2) the hair in the occipital region was matted together from exudation, and (3) the

skin of the neck was swollen and reddened. Following the fourth application five days after the initial one, (1) the itching extended to the interdigital spaces of both hands, to the arms and the soles of the feet. (2) Exudation appeared behind the ears, and the dermatitis progressed in downward extension to the arms, chest, and thighs, where there appeared a decided erythema followed by a generalized eruption.

When the patient was first seen he was suffering from an eruption composed of erythematous, slightly raised patches varying from pea to palm-sized and sharply defined. These patches were scattered all

Fig. 3. Fig. 4.

Fig. 3.—Positive patch test to Liquid Arvon.
Fig. 4.—Positive patch test to liquor potassii arsenatis.

over the body surface, but were more pronounced in the sternal, interscapular, inguinoscrotal, axillary, and umbilical regions. Some of them were annular in shape, and their extreme borders were made up of very small red papules. The plaques were covered mostly by greasy yellowish scales and crusts. The face of the patient was somewhat oily and presented many pea-sized erythematous lesions similarly crusted. The scalp was covered with abundant fine, brawny, slightly greasy grayish scales.

On April 5, 1934, we carried out patch tests with (1) Liquid Arvon, (2) 17 c.c. of Fowler's solution in 100 c.c. of water, (3) 4 per cent

salicylic acid in 5 per cent alcohol, (4) 4 per cent resorcinol in 5 per cent alcohol, and (5) oil of lavender. Positive patch tests resulted from the Liquid Arvon and the Fowler's solution. Passive transfer was negative.

THERAPY

In 1920, Ravaut[17] recorded the first cases of arsenic dermatitis in which sodium thiosulphate was used as a therapeutic measure. The skin lesions in his cases had followed the use of neoarsphenamine, and this form of treatment was based on the theory that the reaction depended on the toxic oxidation products of arsphenamine in the body. Consequently, a nontoxic reducing agent would be the rational antidote. McBride and Dennie,[18] however, reporting a series of cases in which treatment by sodium thiosulphate intravenously yielded remarkable results, explained the action of the drug on a sounder chemical basis. They maintained that, as previously known, the reaction is due to arsenic and is relatively independent of the type of arsenic compounds used, and argued therefrom that the condition can best be combated by rendering the arsenic inert in some way, such as by precipitating it in the tissues as the insoluble sulphide. Sodium thiosulphate was not used in the case here reported. The patient began to improve about three weeks after the first application of the hair tonic. The improvement thereafter was gradual; it took another three weeks from that point on for complete subsidence of his symptoms of dermatitis.

Bernstein[19] has shown that specific reagins were present in the circulation of a patient with known cutaneous sensitivity to arsphenamine and with an arsphenamine dermatitis. Contrary to his observations but in accord with those by Templeton and Skilling[20] and others, we were unable to show the presence of reagins, for passive transfer proved negative on several attempts.

SUMMARY

A case is reported of untoward effects from arsenic resulting in marked generalized dermatitis from the application of a hair tonic and dandruff remover, known on the market as Liquid Arvon. The allergic nature of the reaction to arsphenamine is indicated in a brief review of the literature. The dangers from hypersensitiveness to arsenic are stressed.

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THE STERILIZATION OF PROTEIN SOLUTIONS WITH MERTHIOLATE*

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FOR a number of years in the laboratories of the University of Illinois, a search has been made for an agent which will sterilize protein solutions without altering or denaturing the protein. The Seitz and Berkefeld filters, while effective in removing the bacteria, leave much to be desired in that they also remove appreciable amounts of protein. They are slow in action and require cleaning and sterilizing. Fruit extracts offer an additional difficulty because of the presence of pectin which rapidly clogs the filter pores. Cooke and Stull[1] have shown that five successive filtrations of a pollen solution will remove all the antigen from solution.

The ideal sterilizing agent for protein solutions used for allergic skin tests and treatments would be one which when added to the material would sterilize it without denaturing the protein, and without irritating effect on the skin. The closest approach to this goal has been attained by the use of merthiolate.

Merthiolate is the sodium salt of ethyl mercuri thiosalicylic acid ($C_2H_5Hg_4COONa$). It is colorless and odorless in solution and has its maximum effectiveness in slightly alkaline media (pH 7.2 to 7.4). Merthiolate is effective in destroying bacteria even in the presence of large concentrations of protein. Powell and Jamieson[2] found that for five-minute exposures merthiolate was germicidal in concentrations of 1:3,000 for *B. typhosus*, 1:4,000 for *S. aureus*, and 1:10,000 for the gonococcus. According to these authors it does not alter the antigenicity of bacterial proteins. Doses of 50 c.c. of a 1 per cent solution have been given intravenously in human beings, and as much as 180 c.c. has been given in divided doses without ill effects.

In order to determine the lowest concentration at which merthiolate will destroy all organisms, a series of tubes was set up containing 10 c.c. of 1 per cent egg albumen in buffered saline (pH 7.2). Since some of our materials are prepared in glycerin solution, a 50 per cent glycerin series (5 c.c. glycerin plus 5 c.c. 2 per cent egg albumen in pH 7.2) was prepared.

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These tubes were all inoculated with a relatively old culture of the hay bacillus (containing spores). The hay bacillus was used because of its resistance to sterilizing agents.

Merthiolate in slightly alkaline buffered solutions was found to be an effective sterilizing agent for the hay bacillus in concentrations up to 1:3,000, both in plain buffered saline and in glycerin solutions. The solutions were sterile within twenty-four hours.

To determine whether the presence of 1:3,000 merthiolate merely inhibits rather than destroys the organisms, the tubes were subcultured every twenty-four hours for two weeks. From time to time broth cultures were made, and these in turn were subcultured on agar plates in twenty-four, forty-eight, and seventy-two hours. No growth was present when the organisms had been exposed to merthiolate up to a 1:3,000 concentration, indicating that the organisms were actually destroyed.

After three weeks', five weeks', and three months' exposure to merthiolate, precipitin tests were made, using an anti-egg albumen serum. The egg albumen exposed to merthiolate (the 1:1,000, 1:2,000, and 1:3,000 concentrations were tested) gave precipitins up to and including the 1:1,000,000 tube. The same result was obtained by the use of the egg albumen solution which had been injected into the rabbit originally to obtain the antibodies. The tests were controlled with buffered saline, and egg albumen 1 per cent in buffered saline. The saline alone gave negative results, while the 1 per cent egg albumen, of course, also came down in the 1:1,000,000 tube. The conclusions were that 1 per cent egg albumen is not altered or denatured by exposure to merthiolate in concentrations up to 1:1,000.

The one drawback that was expected from the use of a chemical sterilizing agent sufficiently potent to destroy organisms was its possible irritating effect on tissues, especially when injected intracutaneously. To test this property, 18 pollen sensitive patients were tested intracutaneously with various concentrations of merthiolate, from 1:1,000 to 1:100,000. It was found that no evidence of skin irritation was present at the site of the intradermal injection with dilutions of 1:75,000 or above. In dilutions of 1:50,000 or less, irritation of the skin was present at the site of the intracutaneous injection.

Based on these results the following method has been adopted in the Allergy Clinic of the University of Illinois for the sterilization of protein solutions. A buffered salt solution with a pH of 7.2 is used as a solvent for the protein material. To this, merthiolate 1:100 is added to make the concentration 1:3,000. This is left for twenty-four hours at room temperature for sterilization. Sterile glycerin is then added to make a 50 per cent glycerin concentration. The result is a primary dilution of the merthiolate in the stock material to 1:6,000. The protein solution is then made up to the desired testing concentration by

diluting with a buffered salt solution of pH 7.2. The strongest concentration used (1:10) results in a merthiolate dilution of 1:60,000. In the majority of cases a 1:100 of the stock material is used with a resulting merthiolate dilution of 1:600,000.

CONCLUSIONS

1. Merthiolate is an effective sterilizing agent in slightly alkaline solutions.
2. In concentrations of 1:3,000 it destroys the hay bacillus in twenty-four hours.
3. It does not denature proteins when used in concentrations up to 1:1,000.
4. It is not irritating when used for intracutaneous tests in dilutions greater than 1:75,000.
5. It can be used to sterilize stock protein solutions used for skin testing.

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COMPARISON OF PATHOLOGIC CHANGES OF INFANTILE ASTHMA WITH ASTHMA OF LONG DURATION

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AMONG the autopsy reports of Huber and Koessler[1] there was a sixteen-month-old child whose asthma had been of five months' duration. In this case the diagnosis bronchial asthma was questioned because of the presence of a large thymus and other earmarks of so-called status thymicolymphaticus. There are no autopsy reports of asthmatic death in the literature in which the disease had been of lesser duration. This brings up the question whether or not asthmatic individuals die of asthma itself during its earliest stage, or whether the findings at their deaths are so distinct from the usually described autopsy changes in asthma that they are not held representative of this disease. This latter thought is more forcibly brought to mind since in the above mentioned case in which the duration of asthma was the shortest, the diagnosis was uncertain. Life insurance statistics,[2] on the other hand, indicate that people with asthma are the more prone to die from it, the shorter the duration of illness had been. According to this, asthma could be expected to be fatal more commonly among young children and infants than in adults.

In reviewing the autopsy material of the Children's Hospital of Michigan, two cases of true allergic asthma were found in which the disease had lasted three and six weeks respectively. One of these children was a boy, six months old, who had a definite family background of allergy and had previously been suffering from eczema. During the whole course of the disease he had been under observation in the hospital. The other, a boy of three months and four days, had also had a family history of allergy. He was clinically sensitive to several foods. The attacks had been present continuously for about six weeks until the child died. Since these cases are reported in detail elsewhere,[3] I wish to limit this discussion to the description of those changes which distinguish this type of asthma from the ordinary case.

Outside of the presence of a general hyperplasia of the lymphoid tissue of the respiratory and gastrointestinal tracts, the only remarkable changes were noted in the lungs. Table I contrasts these changes with those described in the usual case of asthma.

These data, I believe, permit certain conclusions which are of definite importance in our understanding of allergy. If an antigen has

contact with the lung tissue, regardless of whether it is carried there by the air passages or by the blood stream, various physiologic actions aid in its elimination or destruction: The continuous flow of mucus over the bronchial lining, the ciliated epithelial cells, as well as muscular contractions, aid in its expulsion from the air passages, the goblet cells of the bronchi, and the immigration of leucocytes in its destruction. In the asthmatic adult there is evidence of an enchancement of this defense mechanism. By the hypertrophy of their mus-

TABLE I

PULMONARY FINDINGS

	IN INFANTILE ASTHMA	IN ASTHMA OF LONG STANDING
Macroscopic	Little emphysema. Bronchi contain little mucus. Cut surface moist. Serous hemorrhagic exudate. Peribronchial lymph glands enlarged.	Emphysema marked. Bronchi occluded by thick mucus. Cut surface dry. Bronchial walls thickened
Microscopic		
Bronchi		
Lumen	Mucus scanty. Little invagination.	Occlusion by mucus and necrotic material.
Epithelium	Intact.	Degenerative changes. Infiltration with leucocytes.
Submucosa	Muscular hypertrophy not noticeable. Lymph follicles markedly hyperplastic.	Muscular layer hypertrophic. Basement membrane thickened.
Mucous glands	No hyperplasia.	Hyperplastic.
Alveoli	Capillary congestion. Edema. Extravasation of blood. Degeneration of alveolar cells. Traumatic emphysema alternating with atelectasis.	Emphysema.
Cellular elements	Lymphocytes prevailing. Subsequent leucocytic infiltration of edema. Few eosinophiles.	Leucocytic infiltration of bronchi. More marked eosinophilia.
Probable cause of death	Edematous hemorrhagic lesions. Bronchopneumonia.	Obstruction of bronchi by mucus.

culature (Huber and Koessler[1]), the bronchi are enabled to contract more effectively. The enlargement of mucous glands procures a greater ability to provide for production of mucus. The presence of polymorphonuclear leucocytes and eosinophiles in the bronchial walls and in their lumen, suggests that an effective defense is taking place by either phagocytosis or a chemical attack upon the invading antigen. In addition, the stretching of the alveolar walls as noted in intense emphysema probably contributes to the inhibition of absorption of solid antigenic materials through the air passages. Evidence points to the fact[4] that absorption of solid materials in the lungs is effected by means of phagocytosis by the epithelial cells through the lym-

phatics about the blood vessels. While experimental evidence on the influence of emphysema on this process of absorption is lacking, it is held likely that through the stretching of the alveoli the lymph spaces are compressed and thus absorption of solid materials is inhibited.[5] Thus, it appears that during an asthmatic attack various defensive mechanisms are at play which are concerned with the elimination of damaging antigenic material. The findings in the above two cases indicate that this defensive physiologic mechanism has not yet developed in asthma of short duration. Instead of the hypertrophy of bronchial musculature and of mucous glands, instead of effective leucocytosis, and instead of emphysema, there is an edema in the alveoli with such vascular changes as were described by Young and Kline[6] in the so-called "irreversible" allergic lesions. These authors found changes of an inflammatory character characterized by leucocytic infiltration and edema associated with necrosis in various organs of the system such as the appendix and the gallbladder. They consider these changes a nonbacterial allergic process and liken them to the inflammation which is observed following repeated injections of horse serum, the Arthus phenomenon. These lesions either may be the cause of death in themselves if they are sufficiently extensive to interfere with respiration, or may become subsequently infiltrated with leucocytes, thus clinically producing the picture of bronchopneumonia.[7] Obstruction of the bronchi by mucus apparently plays little, if any, part in the production of death.

In comparing this condition with the pathologic findings described in experimental anaphylaxis in dogs, one can readily recognize a striking resemblance. The exudative capillary lesions were classically described by Dean and Webb[8] in the lungs of anaphylactic dogs and by Dean[9] in a case of anaphylactic shock in the human being following an injection of horse serum. Indeed, a comparison of the pulmonary lesions in our cases shows a much closer resemblance to those described by these authors than it does to asthma of long standing.

If this is true, these data would establish a missing link for those who consider anaphylaxis and allergy essentially identical.[10] Human anaphylactic shock could then be interpreted as a pre-allergic condition, during which the system has not had a sufficient chance to adjust itself to the suddenly invading antigen to which sensitivity exists, while in an asthmatic attack there is an inherited or possibly acquired tendency to delay the absorption[11] and to eliminate or destroy such damaging antigens promptly. On the basis of this reasoning we could thus understand some of the apparent discrepancies concerning the distinction of anaphylactic and allergic phenomena. It is well known that skin reacting antibodies (reagins) have not yet been clearly demonstrated in human anaphylactic shock,[12] while they are easily

demonstrable in fully developed asthma. The lack of protective reactibility in shock as compared with asthma of long duration is possibly associated with the absence of reagins.

SUMMARY

In two cases of infantile asthma of three and six weeks' duration respectively, the autopsy changes resembled more closely those of anaphylactic shock than those of asthma of long duration. A tabulation of the outstanding pathologic features is presented.

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10 PETERBORO

Annual Review

PROGRESS IN ASTHMA

Literature for 1934 and 1935

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THE periodic literature on allergy has become so extensive that it has been found necessary to discuss one phase at a time. The present review concerns itself entirely with the subject of asthma. The articles dealing with asthma published in the last two years number several hundred. In this review it has been found advisable to select only those papers which present some new phase of the subject or those which present data contradicting the old. As a general rule, articles which demonstrate corroboration of previously presented facts are excluded from this presentation. The almost complete absence from this review of a discussion of papers dealing with specific diagnosis and treatment is intentional: the facts are so well established that it is the feeling of the reviewer that nothing will be gained by their inclusion here. Papers dealing particularly with pollen allergy and articles whose chief emphasis is on children are ignored in this discussion because they are to be included later in special reviews.

PATHOLOGY AND LABORATORY STUDIES

Several autopsy studies have been added. Michael and Rowe[1] studied two fatal cases of bronchial asthma and report changes similar to what others have found. There were hypertrophy and hyalinization of the basement membrane with eosinophilic infiltration in the mucosa of the maxillary sinus. One patient had tough mucous plugs occluding most bronchi. A probable myositis of the bronchial musculature is also an additional pathologic change described. Bubert and Warner[2] describe a definite thickening of the bronchial musculature in a sixty-nine-year-old woman, with a history of asthma of two years' duration, who died in an asthmatic attack.

On the basis of the autopsy findings in two infants who died three and six weeks, respectively, after the initial onset of their asthma, Waldbott[3] claims that there is a decided difference in the lung changes from those in adults. The most noteworthy findings were edematous

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hemorrhagic areas in the lung, lymphocytic infiltration, absence of marked bronchospasm or emphysema, and the presence of very little mucus in the bronchi. These changes simulate more nearly those produced in anaphylaxis, particularly in the dog; apparently the same stimulus later in life produces entirely different pathologic changes. The author believes that these facts lend support to the theory of the identity of anaphylaxis and atopy. The pathologic findings in the asthmatic adult may be interpreted as being due to the gradual development of a protective physiologic mechanism serving to counteract the shocking influence of the antigen.

Söderling[4] cites cases which illustrate that certain complications of asthma occur which may be mistaken for other conditions. The most important of these are: pleural changes, consisting of fibrous adhesions and fibrous bands and which are often suspected as tuberculous; parenchymatous lung changes, usually due to atelectasis and bronchiectasis, without any typical asthmatic picture. Binhold[5] finds the heart volume decreased in asthmatic persons, except during acute attacks. Emphysema increases the heart volume to the upper limits of normal.

In studies on bronchial asthma in children, Bauer-Albrechtson[6] finds a slightly decreased blood sugar with normal phosphorus and calcium. Blood platelet counts were normal in 17 patients observed during, before, and between attacks of asthma. This is confirmatory of the work of Crandall and Feinberg[7] who previously had reported the level of inorganic serum phosphorus in fasting children and adults to be within normal limits. The latter authors point out that reports which cite markedly diminished phosphorus values may be due to the use of anticoagulants. During acute asthmatic attacks, Drilhon[8] claims to have found serum calcium values of 25 mg. to 28 mg. per 100 c.c.

The controversy concerning the sedimentation rate of the erythrocytes in allergy is reopened by Ellis[9] who argues that the accepted normal range has been established from studies which did not exclude allergic individuals. When the latter precaution is taken, he finds that the rates in allergic conditions are all slower than normal. He studied 30 asthmatic and 60 hay fever patients. He emphasizes the fact that the rates in women are faster than those in men.

Furonaka and his coworkers[10] found the water and chlorine content of the peripheral blood diminished during asthma attacks; the values returned to normal after relief with adrenalin or spontaneously. With the appearance of the asthma attack the blood sugar increased slightly, while the blood lactic acid diminished slightly. After adrenalin or "Asthmalysin" both were definitely increased.

In experiments on dogs with the production of expiratory dyspnea by a ball-valve mechanism in the trachea,[11] emphysema was produced.

As a result of the expiratory delay and overdistention of the alveoli, eosinophilia (4 to 18 per cent) was obtained. The evidence indicates that the response is specific and is of a reflex nature. Adrenalin did not affect the eosinophilic index. The authors conclude that acidosis is not the causative factor in eosinophilia. They believe that eosinophilia, per se, is not pathognomonic of allergic disease.

ASSOCIATED CAUSES AND DISEASES

Whether tuberculosis and asthma are in any way associated is discussed again. Fraenkel,[12] in a routine examination of 369 asthma cases (in London), finds 16 instances of active tuberculosis and 46 inactive. He calls attention to the possibility of pulmonary tuberculosis masquerading under a clinical picture of asthma. He thinks also that active tuberculosis, due to marked allergy to the tubercle bacillus, may be a natural step in the evolution of an asthmatic who is allergic first to other substances. On the other hand, Bray[13] concludes that there is no close relation between asthma and tuberculosis, on the basis of evidence obtained from clinical statistics, x-ray and tuberculin reactions. He finds that only one asthmatic patient in 100 gives any positive evidence of active tuberculosis; only one patient with active tuberculosis in 200 suffers from asthma; and, when asthma develops in a tuberculous subject, the sensitizing agent is generally of an inhalant nature, and the asthma is relieved by its removal or by a course of specific desensitizing injections.

An asthmatiform syndrome or even true asthma with local eosinophilia may be produced by syphilis of the lung.[14] Four such cases are described. Evidently the symptoms are produced by tracheobronchial adenopathy or by syphilitic bronchitis and peribronchitis or even true sclerosis of the lungs. Further confirmation is given by König[15] on the infrequent association of diabetes mellitus and bronchial asthma. Among 1,240 diabetic patients he encountered only three instances of asthma. He cites references which indicate that among asthmatic persons there are very few diabetics, 6 out of 4,000. He thinks that this may be explained on the basis of an antagonism between insulin and adrenalin.

The disappearance of asthma during pregnancy is a frequent clinical observation. Green,[16] on the other hand, presents two cases in which pregnancy aggravated or caused the asthma. He concludes that in a patient with true bronchial asthma of anaphylactic origin the attacks are markedly exacerbated by pregnancy. He says further: "In the types of asthma directly related to the sexual cycle, attacks may appear with each menstrual period, be absent during pregnancy and lactation, and recur with reestablishment of menses. . . . Attacks may

occur only during pregnancy or even only during pregnancy with a child of one sex and not with the other."

Cooke and Grove[17] stress the rôle of sinus infection in asthma. In 248 patients with infective asthma whose age of onset was after ten years, sinus infection was a causative factor in 92 per cent. They believe that an allergic reaction to the bacteria or their products is the cause of infective asthma. As support of this idea they call attention to: (1) the familial history of allergy, (2) other allergic manifestations in the patient, (3) eosinophilic response of sinus mucosa, (4) eosinophilic content of nasal and bronchial secretions and blood, and (5) production of systemic reactions by vaccine injections.

Several reports touch upon the subject of atmospheric changes in relation to asthma. Evers and Schultz[18] call attention to the connection between weather changes and asthma. This occurred even in their comparatively asthma-free resort. Among factors which apparently give trouble are increased moisture of air and change in barometric pressure. Wolfer[19] (Switzerland) finds that high altitudes are beneficial in asthma. He says that the ventilation of the lungs increases with increasing altitude. The change in pH might be a factor. Several other factors might play a part. Most important, probably, is the cleanliness of the air: molds and yeasts are rare. Milk when exposed does not thicken nor does meat spoil. The dryness and the mechanical cleanliness of the air help the bronchitis. A controlled room with low humidity and constant temperature had very little influence on the onset of pollen asthma following a storm, according to Rappaport and his coworkers.[20] Increased ozone had no effect.

While asthma is seldom fatal, Dublin,[21] in analyzing mortality rates from insurance files, finds that the mortality risk is between 27 per cent and 63 per cent of the normal. Build is an extremely important factor. Underweight asthmatic persons have double the expected death rate and those overweight have one and one-half times, by the American Men Table. The excessive mortality of asthmatic individuals is due primarily to myocardial disease and to respiratory affections, particularly pneumonia. The rate is especially high among asthmatic persons whose condition is complicated by emphysema or bronchitis.

STUDIES IN CONSTITUTION

The mystery of the constitutional basis for allergy still remains unsolved. Perlroth[22] says that laboratory experiments with various concentrated allergens do not disprove the constitutional theory, for in nature no such concentrated allergens exist and only predisposed individuals react to allergic influences. In the unhealthiest regions of Holland only 2 per cent to 3 per cent of the population suffer from allergic diseases. It is not denied, however, that exposure is important. In studying the age-sex incidence of allergic conditions, Nelson[23] found

a preponderance of males in the first decade of life. In the second and third decades there was a preponderance of females.

In an attempt to determine a possible physical make-up for asthmatic children, Young[24] studied 368 asthmatic persons of ages six to twelve years and compared them with control groups. He concluded that averages of practically all absolute physical measurements are normal, with the possible exception of the anteroposterior diameter of the chest—which might, of course, be an effect of the asthma. Asthmatic children show a relatively greater excess of the blond-haired type. His elaborate article detailing every possible measurement, with negative results, should be considered a definite answer to the question of body build in relation to asthma.

The strict adherence to a constitutional explanation for allergy has been somewhat weakened by reports of some recent work. Vaughan[25] made a house-to-house survey of a community of 508 individuals and found that in addition to the 10 per cent who gave a history of major allergic symptoms there were 50 per cent who told of occasional occurrence of definite allergic symptoms or more frequent occurrence of lesser symptoms. On the basis of these findings, Vaughan says that the difference between major and minor allergics depends chiefly on the degree and frequency of contact with the offending allergen. Recognition of the allergen depends upon this and determines into which class the individual will fall. The difference between the allergic and the so-called normal is more quantitative than qualitative. Salén and Juhlin-Dannfelt[26] studied the cutaneous reactions of 432 persons belonging to different occupational groups. A large number reacted to the allergens to which they were exposed. They say that this frequently occurring latent allergy necessitates a modification of the usual idea that positive cutaneous tests always imply clinical manifestation of allergy. The question should no longer be raised as to why some individuals become sensitized, but rather why some sensitized persons have clinical manifestations and others do not.

THE NERVOUS SYSTEM

Tsuji[27] says that vagotonia does not play a causative rôle in asthma; this is evident from the failure or minimal effect of vagotomy and atropine. The most effective remedies against the asthma attack are adrenalin, pituitrin, and ephedrine, those, as animal experiments show, that cause contraction of the lung capillaries and thickening of the capillary wall. The effectiveness of nitrites, diuretin, papaverine, and sympathectomy is due to the fact that by these procedures the reflex spasm of the lung veins is ameliorated, and therefore the asthmogenic substances which have been kept in the lung capillaries are allowed to pass through the left heart. Handa,[28] on the other hand, claims that bronchial asthma is a vagus neurosis of the respiratory organs. He

explains the action of ephedrine and epinephrine as that of causing an increased tonus of the sympathetic nerves, thus overcoming the excess of vagotonia. He regards endocrine disturbances as playing a dominant rôle in this imbalance. Gudehus[29] has practically similar views as the latter author.

The psychic factor in asthma is stressed by a number of authors. Freudenberg[30] says that among asthmatic children one may frequently observe those with a marked inferiority complex and a desire for recognition and attention. The author cites the case of a boy eleven years of age who had had asthma since he was three years old. He was sent to a health resort where he was free from attacks, but relapsed as soon as he was home. His asthma became much worse after the birth of a sister. The author thinks he used his attacks as a means of centering his mother's attention on himself. He cites another child, a girl of eight years, who held herself in a breathless state of tension, in a desire to excel her older brothers and sisters. There was a family history of asthma.

Jolowicz[31] stresses functional disorders in asthma. He cites several cases among which are the following: A forty-year-old woman teacher who had had asthma for years was stricken with an attack accompanied by fever. Psychoanalysis revealed a religious fanaticism. After treatment and establishment of insight into her affair, she coughed up some of the products of her bronchopneumonic patches, and the fever subsided on the same day. Another case was that of a sixteen-year-old boy who had frequent attacks of asthma. Examination revealed a close maternal attachment. The asthmatic attacks were cured only when the boy went to college and had affairs with other women. Other cases cited are: a man who was cured by the fear of receiving a hypodermic injection; a thirteen-year-old boy who had attacks only on Saturdays and Sundays, and whose trouble was traced to the influence of a psychoneurotic mother; and a young man whose lifelong asthma was attributed to an overzealous mother.

Obendorf[32] cites in great detail a case of apparent asthma in a neurotic young woman who had a neurotic family background and environment. Significant points in the history were a neurotic and bedridden mother, a socially unsuccessful father, and an incompatible husband who also had hay fever. The author thinks that the asthma "is a manifestation of a conflict concerning emission and reception, domination and submission, unconscious masculinity and conscious femininity." The patient died during an attack of asthma.

Space does not permit a more complete discussion of these and other papers dealing with the mental state. Even a superficial analysis of the case reports cited discloses much more logical explanations for the symptoms than the psychic influences claimed. The family history of

allergy is disregarded by these authors; the effect (other than psychic) of environmental change on the basis of allergens is not even mentioned; organic findings, such as bronchopneumonic patches, are glibly explained on a psychic basis. An asthmatic patient apparently may even die during an attack induced by a mental state! Most of these authors choose to disregard entirely the possibility of factors other than mental. While it may be conceded that nervous and emotional stimuli do play a part in the ups and downs of an asthmatic person, there is reason to doubt that a pure "nervous asthma" occurs even infrequently. It is my firm opinion that if any real progress is to be made on the question of the relation of the nervous system to asthma it will have to be made in work done under the direct supervision of asthma or allergy specialists and not psychoanalysts.

The question of nervous asthma is quite well summarized in the terse words of Dekker:[33] "There is no nervous asthma. Behind every asthma stands an allergen. Constitution plus allergen produces sensitization. Attacks may be precipitated by nonspecific things. It is not denied that the vegetative nervous system, the psyche, or reflex vagus stimulation may play a rôle, but only then when the body is sensitized can these be effective. Only allergic asthma is asthma. Only by sticking to this view can we overcome our pessimism. This is necessary if we are to succeed."

IMMUNOLOGIC STUDIES

Satisfactory advancement has been made in basic studies on the immunology of allergy and its causes. I shall recount here only a few of these reports, since the subject will be covered more fully in a later review on immunology. A strong ray of light has been thrown on the mystery of the house dust allergen by Cohen and his coworkers.[34] They found that the house dust allergen developed in cotton under any of the conditions studied, such as exclusion of air, sterilization and exclusion of bacteria and molds. They conclude that the house dust allergen is developed in the process of ageing of cotton, possibly by an autoenzyme. Tuft[35] continues with his studies on serum allergy. By passive transfer and cross neutralization experiments with serums containing both horse dander and serum reagins he shows that desensitization to horse dander desensitizes to serum, but not vice versa. From these and clinical observations he concludes that horse dander contains two antigens—the dander antigen and a small amount of the serum antigen.

Brown[36] observes that decomposed, fermented, or autolyzed proteins are more prone to act as allergens than are fresh, unchanged, or normally digested proteins. Green fruits and vegetables as ordinarily obtained have had hours and days of exposure to temperatures that

promote chemical change. Canned fruits and vegetables are generally exposed a short time between picking and canning—which may make canned foods less allergenic. Fresh foods may undergo spoiling in the gastrointestinal tract. He thinks that in some cases a mild intestinal stimulant taken with food may prevent allergic reactions by increasing peristalsis, increasing digestion, and inhibiting bacterial putrefaction.

Since the complement content of the blood is thought to be an expression of colloidal conditions, and since allergy is considered by some to be bound up with altered colloidal states, Paul and Pelyi[37] thought it likely that allergic conditions would show an alteration in the amount of complement. Their theory was verified by the finding of a decreased amount of complement in the serums of allergic patients. On the other hand, Tilden,[38] working independently on allergic patients from my clinic, found a complement titer ranging between 0.02 c.c. and 0.06 c.c., with an average value of 0.05 c.c. These figures were entirely normal when compared with the findings in over 100 controls.

Experiments with pollen cases and other types of cases by Black and Shelmire[39] indicate that the activity and specificity of the urinary proteose of Oriel may be due to the unchanged antigen which has been eliminated in the urine.

Basic information on the question of the development of hypersensitiveness in man has been furnished. Simon and Rackemann[40] gave repeated intracutaneous injections of guinea pig serum to several persons and found that the entire skin of these people became sensitized. The first sign of sensitiveness was a delayed reaction of the tuberculin type; with further injections an immediate reaction of the wheal and erythema type resulted. Clinical sensitiveness was not produced in any of the individuals. There was no difference in this artificial sensitiveness in atopic and nonatopic persons. Atopic reagins were found in only one individual, and he developed a high degree of sensitiveness. The authors think that if the degree of sensitiveness were high enough all would have reagins. They think, therefore, there is only a quantitative and not a qualitative difference between natural and artificial sensitization. Brunner[41] reports, however, that in a series of 40 atopic and nonatopic persons it was almost impossible to sensitize by repeated subcutaneous injections.

Further studies were made by Simon and Rackemann[42] in 9 atopic persons. Guinea pig serum was packed in the nose at intervals varying from four days to two weeks. In all of them, symptoms of vasomotor rhinitis developed after a few treatments. At first the reactions were delayed; later they became immediate. At the same time the skin also became hypersensitive to guinea pig serum as determined intracutaneously.

Colmes and his coworkers[43] studied 32 bakers by intradermal tests. Of these, 15 reacted to flour and 8 to ragweed pollen. Only one individual was clinically sensitive to flour. They conclude that clinical hypersensitiveness is not determined wholly by heredity or by the frequency and degree of exposure or by the vulnerability of the shock organ. To become sensitive, they say, is a common property of mankind. The capacity to express the sensitivity clinically is the property of those in whom the intrinsic factor, the activator, is operative. Salén and Juhlin-Dannfelt[26] report similar experiences with skin tests in occupational groups.

RESPIRATION

From observations made on the total pulmonary capacity and its subdivisions during acute asthma, Hurtado and Kaltreider[44] conclude that during the acute distress there is a relative and absolute decrease of the vital capacity with marked increase in midcapacity and residual air. Shortly after epinephrine administration the vital capacity increases and the midcapacity and residual air decrease. The improvement or disappearance of symptoms is coincident with the changes. Weltz[45] finds that the breathing during the asthmatic paroxysm is the same as that in any other type of bronchial stenosis.

Prinzmetal[46] reports some enlightening experiments in this connection. He found that bronchoconstriction in dogs caused an increased inspiratory position of the chest, pulmonary distention, and a more negative intrapleural pressure. In four cases of active asthma the intrapleural pressure was more negative, indicating increased active inspiratory distention. His experiments in dogs show that the prolonged effect of more negative intrapleural pressure causes distention and stretching of the lungs with probable loss of elasticity. Thereafter the intrapleural pressure rises and the weakened alveolar walls, subjected to further strain, rupture and coalesce. The increased carbon dioxide tension and anoxemia also cause more negative intrapleural pressure and distention of the lungs. He concludes that "the greater negative intrapleural pressure found in bronchoconstriction may be explained by increased resistance to respiration, carbon dioxide retention, and anoxemia resulting from bronchoconstriction."

In a study of cardiac asthma, Harrison and his coworkers,[47] established the following points. The dyspnea of cardiac asthma is not usually associated with abnormalities in oxygen, CO_2, or pH content of arterial blood. The relief of the seizure by morphine is not usually associated with constant changes in blood gasses but is usually followed by a decrease in ventilation and an increase in the vital capacity. They feel that pulmonary congestion is the probable underlying cause of cardiac asthma. Precipitating causes are those which produce increased ventilation: deep breathing, cough, fear, unpleasant dreams,

and abdominal distention. The same factors which cause cardiac asthma by night may cause seizures during the day and result in more or less continuous dyspnea.

DIAGNOSIS

Clarke[48] emphasizes the importance of early diagnosis of allergic disease of the respiratory tract, especially in children. Before dyspnea begins there are usually prolonged premonitory symptoms such as sneezing, blocked nose, mouth-breathing, cough, and coryza. The acute dyspnea attack often is the first thing which calls attention of the family and doctor to the allergic nature of the ailment. Much better results are obtained if an early diagnosis is made. Clarke thinks that pneumonias are frequent in asthmatic children, are caused by type IV pneumococcus, and are generally much milder than in non-allergic persons. The diagnosis is frequently overlooked and the disease called either bronchitis or influenza. The pneumonia and perhaps the bronchitis frequently leave pleural adhesions which interfere with respiratory activity and predispose to further attacks of bronchopneumonia and pleurisy. The result is that there is frequently produced a permanent deformity of the lower lobes with fibrous tissue formation and pleural adhesions. This can sometimes be demonstrated on physical examination as slight dullness and moist inspiratory râles.

I have emphasized[49] the fact that allergy is so widespread and that it affects and permeates the practice of every practitioner and specialist to such an extent that the subject cannot be considered as belonging totally to the specialist in allergy. The general practitioner must learn the principles of allergy and must be able to meet at least the simpler allergic situations.

The importance of specific skin tests is still being debated. I shall not attempt to discuss any of the numerous papers which tell about the results of tests and which give statistical data corroborating old facts with regard to the importance of tests. Those are repetitions of well-known and accepted facts. It is much more to the point to discuss a few of the controversial reports and those that add a little spice to the subject. Rackemann and Simon,[50] in testing 60 normal "nonallergic" persons in a ward by intradermal technic with nine allergens, found that 30 reacted positively to one or more substances. Similar data are apparent from two of the papers quoted earlier.[26, 43] Rowe[51] feels that skin tests are not quite so important as some allergists believe. He stresses the diagnostic importance of trial diets. He feels also that cutaneous tests give more information than intracutaneous tests.

On the other side, we have studies which tend to demonstrate the importance and value of diagnostic skin tests. Stevens[52] compared the sensitivity of the bronchopulmonary tract with the skin

tests, using extracts of inhalants, in a series of asthmatic patients. He found that when the skin failed to react, the lungs seldom reacted. Stewart[53] is even more emphatic and maintains that she is able to make a specific diagnosis in well over 95 per cent of the cases by combining thorough testing with subsequent clinical history. Pediatricians have customarily discouraged the use of diagnostic skin tests in young children and infants because of the conception that the young skin fails to react. Carey and Gay[54] have attempted to determine whether infants' skin is reactive. Using infants of ten weeks or younger, they sensitized their skins with serum containing ragweed reagin. Subsequent tests with ragweed antigen showed reactions just as frequently as in adults, although stronger antigens were required to give the same degree of reaction.

A new method for the diagnosis of allergy to a specific food is described by Vaughan.[55, 56] This consists of a leucopenic response, usually forty-five to ninety minutes after the ingestion of the food. A number of papers dealing with this phase of specific diagnosis have appeared since. These will probably be discussed more fully in a later review.

ATOPENS

General.—As discussed above, very interesting studies have been made on house dust[34] and on horse serum.[35] Sensitization to the hairs or outer cells of wheat is described by Duke[57] as the commonest cause of cough and asthma among wheat-flour millers. Blumstein[58] discussed buckwheat sensitivity. Among 500 allergic patients, 19 were found to be skin sensitive to buckwheat. Of these, 8 were clinically sensitive, mostly by inhalation. Most instances were in bakers or those associated with the baking industry or in housewives. Duke[59] calls attention to the numerous uses of soy bean and its products and reports five patients who had asthma from contact with the soy bean at a mill in which they worked.

A case of asthma due to locusts[60] has been described. Fisher[61] reports the case of a wife of a beekeeper who reacted to bee stings by attacks of asthma and urticaria. He desensitized her successfully by injections of extracts of whole bees. Parlato[62] continues with his investigations on the caddis fly. In a series of 850 allergic patients, 43 gave positive reactions to this fly. Of these, 32 were treated and, of these, 30 received complete or almost complete relief. In another report[63] he indicates that the caddis fly may be found along the Great Lakes and the several states and parts of Canada which border on them. They may be found also along other lakes and rivers. The presence of their emanations can be definitely established by the examination of exposed slides. These emanations have been found in various places in Buffalo, but none were found six miles away from the lake. The

various species of the fly give a similar immunologic reaction. In Buffalo the season is about the middle of June to the first part of September, reaching a maximum about the middle of August.

The common use of pyrethrum as an insecticide is responsible for frequent mysterious allergic respiratory reactions. The relationship of pyrethrum to ragweed pollen makes the former an important allergen. In a series of 225 patients sensitive to ragweed pallen, I have found[64] an incidence of 46.2 per cent of positive cutaneous reactions to extracts of commercial pyrethrum. In another series of 113 allergic patients not sensitive to ragweed, only one gave a moderate reaction to pyrethrum. By passive transfer it was shown that cross reactions could be obtained with ragweed and pyrethrum. Desensitization with one antigen desensitized to the other.

Karaya gum (Indian gum) is reported by Bullen[65] as the causative factor in a vasomotor rhinitis in a woman who used a hair-waving fluid made from an emulsion of that material. I have also described the case of a beauty operator who had a very obstinate asthma which I definitely traced to the Karaya gum in the hair-waving fluid.[66] Lycopodium[67] in the form of a powder used for an oily scalp is described as a cause of vasomotor rhinitis. Chicle in chewing gum[68] was responsible for two instances of allergy. Fondé and Fondé[69] describe what is probably a new cause of hay fever and asthma—the honey dew droplets contaminating the air from insects which obtain it from live oaks.

The case of a ten-year-old girl[70] who had asthma of six years' duration is cited. On observation it became apparent that the attacks followed shortly the eating of paper, a habit which had persisted since infancy. The author obtained a marked reaction from a skin test with paper. Psychoanalytic treatment broke the child of her habit, and she has not had any asthma for several months.

Kibler[71] describes a case of asthma in which apparently the chlorine in the drinking water was responsible for the attacks. An epidemic of urticaria, asthma, and hay fever in people who were accustomed to swim in a certain bathing place was noted by Teuscher.[72] Investigation disclosed a particular growth of *Myriophyllum spicatum* (water milfoil). Tests with extracts of the latter showed positive reactions. Injections with the extracts produced desensitization in about two weeks with disappearance of symptoms. Subsequently the plants were dredged from the water.

Drugs, Serums, Etc.—Two reports concern the production of severe acute asthma due to the use of evipan sodium (barbital derivative) as an anesthetic.[73, 74] A fatal case of asthma is reported from the use of butyn in washing nasal mucosa during local anesthesia.[75] Apparently anaphylactic death in a young male asthmatic patient is attributed to 10 grains of aspirin.[76] I believe that the latter drug

constitutes a real danger, particularly in dealing with allergic patients. I find aspirin allergy extremely common. The unwarranted enthusiasm for the use of dinitrophenol in real and imaginary obesity has resulted in numerous instances of allergic reactions to this drug. The nature of the allergy in most instances has been of the drug type, i.e., with negative skin tests and negative passive transfers. Frumess,[77] however, describes a case of dinitrophenol urticaria in which a positive cutaneous and passive transfer test were obtained.

Friedman[78] cites the case of a six-year-old boy with asthma and eczema who, after an initial injection of diphtheria toxin-antitoxin twenty days previously, received a test injection of 0.05 c.c. of horse serum intracutaneously. Death ensued in eight minutes from anaphylactic shock. It is needless to say that intracutaneous tests with undiluted serum should never be used until a 1:100 or even weaker solution is used first. The question of horse serum sensitivity, the relation to serum reactions, and the question of relationship between horse dander and serum are questions of vital importance in this connection. Of the more recent papers on this subject it is suggested that those of Tuft[35] and Rudolph and Cohen[79] should be studied.

Szarvas[80] tells of his own sensitization to arsphenamine. Because of an inflamed skin surface on one of his fingers and because he handled syphilitic patients he frequently painted his finger with an arsphenamine solution. The finger continued to become more and more inflamed, and finally the author developed asthma. By eliminating any possibility of the factor of inhalation he determined that the cutaneous and respiratory symptoms resulted from the contact of the arsphenamine solution with the skin.

Insulin allergy is of frequent occurrence. The commonest form is the local reaction at the site of injection. Murphy and his coworkers[81] described two cases of generalized insulin allergy. Successful desensitization to insulin allergy is reported by Bayer.[82] A diabetic woman who became insulin sensitive, reacting by local and generalized urticaria, was desensitized by half-hourly injections, beginning with 1:1,000 of a unit of insulin.

Fungi.—Sensitization to fungi is assuming increasing importance in the recent literature on allergy. A large number of contributions deal with the allergy accompanying fungous infections of the skin; these will not be discussed in the present review. The finding of a large percentage of positive cultures of *Monilia albicans* in chronic asthmatic persons has been reported.[83] These findings, however, are probably of relatively little importance as compared with the growing realization of the prominent part played by nonpathogenic fungi in allergy, chiefly as contacted from the air.

In a series of 600 allergic patients with chiefly seasonal and nonseasonal rhinitis or asthma, Little and I[84] have found 65, or 10.8

per cent, who react to yeast by cutaneous test. Many of these could be proved to be clinically sensitive. While wild yeasts may be contacted by inhalation, the clinical impression is gained that most of the patients were obtaining their symptoms from the yeast ingested—as found in bread, crackers, beer, etc. More recently Biederman[85] has presented case histories of four adults who were sensitive to yeast by ingestion. A very interesting study on the serologic reactions of monilia and other yeastlike fungi is reported by Almon and Stovall.[86] The general impression is gained that by serologic reactions only very marked differences in organisms can be ascertained.

An interesting study on the relation of molds to respiratory allergy was made by Prince and his associates.[87] In trying to explain the reason for the existence of a seasonal group of asthmas occurring from October to March in Galveston, Texas, they thought of the possibility of molds, since during that period the prevailing winds are from the north where marshy lands offer a good breeding place for molds. During June and July, 1933, they exposed daily culture plates and obtained 29 cultures of different molds. Intradermal tests with extracts of these molds were made on 18 individuals of whom 14 had respiratory allergy. Of the latter, 11 gave positive reactions. Good results were obtained with treatment in some of these patients. No figures are presented as to the numbers of molds in the air, and no mention is made of air cultures of the other ten months of the year.

The need for greater attention to the problem of mold allergy was emphasized by me[88] in a paper in which I tabulated the cutaneous reactions to fungus extracts in a series of allergic patients. In 243 patients with respiratory allergy 68, or 28 per cent, gave positive cutaneous tests to one or more of the fungus extracts used. The majority of these fungi were the ordinary molds whose air-borne spores form a ready opportunity to cause inhalant allergy. In the approximate order of frequency of reactions the following were the most common: *Alternaria,* yeast, *Aspergillus, Chaetomium, Penicillium, Monilia,* and *Trichophyton.*

Seven cases of asthma due in whole or in part to fungus alternaria are reported by Underwood,[89] who says that this is probably the most prevalent single-type fungus in Nebraska. No evidence, however, of results of mold cultures or spore counts is presented. Underwood mentions the seasonal character of the attacks and the good results obtained by desensitization, observations which are also recorded in my paper[88] which preceded his.

Since atmospheric fungous spores may play such an important rôle in the causation of respiratory allergic manifestations, it is evident that a more detailed knowledge of the numbers, types, distribution and variation of these spores is necessary. Several studies of the spore content of the air have been made. In the main these have consisted

mostly of sporadic and isolated exposures of slides or culture plates on a few occasions at various altitudes. Thus, MacQuiddy[90] found a large number of spores at an altitude of 4,000 feet near Omaha, Nebraska, and a decreasing number at higher altitudes. Air studies are also reported by Meier and Lindbergh.[91] Lindbergh exposed vaseline-covered slides over various points of his Arctic flight. For example, on one slide exposed on August 6 for forty minutes at an altitude of 3,000 feet above sea level over the coast of Greenland, north of 70° latitude and well above the Arctic Circle, they found 193 objects (spores, pollen, etc.) in a 5 cm. area. In these and similar exposures they found *Macrosporium (Alternaria?), Cladosporium (Hormodendrum), Leptosphaeria, Mycropharella, Trichothecium, Helicosporium, Uromyces,* etc. Proctor[92] reports the finding of molds at altitudes over 10,000 feet. *Aspergilli* and *Penicillia* were the most common but not numerous. Other fungi found were *Rhizopus, Mucor, Oospora, Monosporium, Macrosporium, Tilochlidium, Fusarium,* and *Actinomyces.*

While the above reports of air findings are of interest, the information gained is not sufficient to be of practical guidance in the causal diagnosis or specific therapy of fungus allergy. We have felt that systematic surveys of the spore content of the air are essential in this field of allergy, just as pollen surveys have been found to be of the first magnitude in importance in their relation to our knowledge of pollinosis. Our first attempt has been to make a year's survey of the daily mold spore content of the air in Chicago. Little and I[93] have reported the results of such a survey in a recent paper. Quantitative and qualitative mold counts as determined by daily exposures of Petri plates are presented. The relation of the pollen season to the mold season is discussed and the importance of various types of molds suggested. Preliminary data on slide studies are also presented.

Bacteria.—As described earlier in this review, Cooke and Grove[17] stress the importance of bacterial allergy in infective asthma. They say that cutaneous reactions to vaccines are not reliable. They depend chiefly on systemic reaction by subcutaneous vaccine injection, which they obtained in 38 out of 70 cases tried. Brown,[94] on the other hand, emphasizes the importance of delayed reactions in the diagnosis of bacterial sensitization in asthma, eczema, and migraine. He employs dried bacterial proteins cutaneously and autogenous and stock vaccines intracutaneously. Benson[95] obtains delayed reactions with intradermal injections of normal and pathogenic colon bacteria and their filtrates. He says that these substances behave as allergens. Another report concerning the selection of autogenous vaccines on the basis of intradermal reactions is that of Banks and Beasley,[96] who claim 80 per cent results in the use of these vaccines in the treatment

of asthma. They apparently disregard all other forms of allergens, claiming that all asthma is intrinsic, due to bacterial infection, chiefly of the nose. They obtain their cultures from the turbinates.

While most of the reports deal with the delayed type of reaction, Forman[97] discusses the atopic type of bacterial asthma. He believes that the latter is common, and he makes a diagnosis of such a condition only if he obtains an immediate reaction with an intradermal injection and corroborates it by a passive transfer test. He employs the following organisms: *Micrococcus catarrhalis, Staphylococcus albus* and *aureus, Streptococcus viridans* and *hemolyticus, pneumococcus,* Friedländer's bacillus and B. coli. There are two reports[98, 99] claiming marked benefit from the use of pertussis vaccine in the treatment of asthma. One of them[99] records a high percentage of positive cultures of B. pertussis in chronic asthma or recurrent bronchitis and implies that some cases of asthma are due to this organism.

The above papers are not the only ones which deal with bacteriology or bacterial allergy. However, they express fairly well the general trend and type of reports written on that subject. My own feeling is that in this field of allergy we have progressed the least in the last few years. The general experience with the types of diagnostic reactions obtained, the infrequency of systemic reactions, and the behavior of the therapeutic response lead one to believe that if we are dealing here with an allergen it is certainly different from the ordinary types of allergens to which we are accustomed. Possibly in the preparation of these bacterial substances we have denatured them to such an extent as to fail to produce reactions. Perhaps there is the need for the evolution of a new and entirely different method by which such bacterial hypersensitiveness may be ascertained. At any rate, I am safe in saying that this subject is far from a closed chapter.

While primary physical allergy may be rare, Swineford[100] found that many allergic patients, 201 out of 325 studied, attributed an appreciable amount of their trouble to physical agents. The factors of which a history was taken were: draughts, wet feet, sunlight, exercise, excitement, fatigue, inactivity, external dry heat, cold baths, hot baths, hot to cold, cold to hot, humidity, cold and damp, pressure, blows, and friction. In 63 who gave a definite clinical history, 65 per cent gave positive tests by heat, cold, and light exposures. This paper constitutes an excellent summary of the experience of many of us that physical agents play an important rôle in the form of adjunct or precipitating causes of allergic manifestations.

TREATMENT

The general principles, methods and results of specific management, including elimination and desensitization treatment, are sufficiently firmly established so that the papers dealing with these phases of the

subject add very little to what is already known. These will not be considered here, except to call attention to the fact that a few comparatively new allergens have been employed in specific treatment.[58, 61, 62, 82]

Nonspecific Protein and Shock Therapy.—Numerous articles have been published on this phase of asthma therapy. The majority of them, for one reason or another, are not of sufficient importance to take up our space here. A few of the more stimulating and less shopworn ideas are presented.

Sobhy[101] (Egypt) tells of a patient who had tuberculosis and asthma, received sanocrysin and was relieved of his asthma. This prompted the author to try the gold treatment in nontuberculous asthmatic persons. In all, 61 cases were treated by weekly injections, beginning with 0.05 c.c. and gradually increasing the dose. Usually not more than five injections were given. Improvement appears after the second treatment, and the bronchitis disappears at the end of the series. Fever usually appears in six to twenty-four hours and is never higher than 38° C. (100.4° F.). Most of the patients were nonallergic and, with the possible exception of one, all were relieved of their asthma.

In 1931 Dudan wrote of the good results obtained in treating asthmatics with sanocrysin. Since that time Cruciani[102] has continued with that form of therapy and records successful results in 11 out of 13 cases. From these results and from his experience of roentgenograms in asthmatic cases he is convinced that the great majority of cases of asthma are tuberculous in origin. How strikingly different South American asthma is from our North American varieties!

Nelson and Duckworth[103] experimented with a variety of nonspecific substances, including colloidal sulphur, broth, soy bean, tuberculin, peptone, autovaccine, and cow's milk. They found that their special broth gave the best results, while sulphur was next in efficacy. Colloidal sulphur was used in doses of 0.5 c.c. of 1:10,000 to 1.0 c.c. of 1:1,000. They have refrained from using pyrexia-producing doses. The treatment gives a short time prophylaxis. The usefulness of intramuscular injections of liver extract is described again,[104] and from Odessa we hear evidence of the antiasthmatic action of extracts from skin, muscle, pleura, etc.[105]

Sheldon and Peck,[106] of the University of Michigan, treated 14 cases of intractable asthma with the Kettering hypertherm with from one to four treatments of a temperature of 104° to 105° at weekly intervals. Of these, 6 were markedly improved and 4 showed slight to moderate improvement. Although the symptoms returned in from one to three months, 6 of the patients were restored to gainful occupations. Similar results are reported by Phillips and Shikarny.[107]

Fixation abscess in the treatment of asthma has been reported again. Basso and Fossati[108] were able to stop the attacks in 28 out of 45 patients treated by fixation abscess produced with turpentine injection. The authors warn that this is a painful and drastic treatment and should be considered only in intractable cases.

Using histamine and a typhoid split-protein on separate series of allergic cases, Thiberge[109] reports astounding results. Histamine improved 95 per cent of the patients, while typhoid protein relieved 83 per cent. The latter substance was most effective in pollen asthma, while histamine gave best results in perennial asthma. I have also had experience with the use of this typhoid split-protein in a fairly large series of asthma and hay fever cases. My impression is that this substance is as good as any nonirritating and mild nonspecific remedy, but no such striking results were observed as recorded by Thiberge.

Israel and Jacob[110] stopped an asthmatic crisis with cutaneous applications of histadin hydrochloride, 1:25, on a series of scarifications on the skin.

Autohemo- and Autoserotherapy.—Autohemotherapy is again recommended. Maddox and Back[111] found best results in children, in all 24 of whom some degree of improvement resulted. In adults the results were not so good. The treatment consisted of five weekly injections of 10 c.c. of blood.

A modification of hemotherapy has been described by several writers. Jacquelin and Bonnet[112] inject the patient's own serum into the mucous membrane of the inferior turbinate, with the production of a bleb. The injections are given daily for 20 doses beginning with 0.2 c.c. and increasing to 0.5 c.c. In a series of asthma patients the results were good in the majority. The authors say that this treatment should be reserved for the more severe cases. Very satisfactory results are also reported by Levin[113] with the same method. In 55 per cent cure was effected, and in 35 per cent improvement resulted. In another series of cases Moruzzi[114] found similar results.

Surgery.—The question of tonsil infection in relation to asthma is again argued. Cooke[115] thinks that tonsils, adenoids, and sinus infection play a frequent rôle, and he believes in the efficacy of tonsillectomy and adenoidectomy. Although admitting that of 108 asthmatic children seen by them 81 were of allergic and only 21 of bacterial origin, Bates and Freedman[116] believe that tonsillectomy helps many patients. Clarke, on the other hand, minimizes the importance of the tonsils.[48] I believe that I am expressing the opinion of the majority in the field of asthma when I say that allergic rather than infectious asthma is the rule in children and that the removal of tonsils seldom has effect other than such temporary improvement as may be ascribed to nonspecific influence from traumatized tissue or anesthetic.

Of 120 asthmatic persons with sinus disease who were treated surgically and subsequently observed from six to forty-two months, Cooke and Grove[117] found 70 per cent had improved. In those with incomplete operations 39 per cent improved, while in those with complete surgery (ethmoids, sphenoids, and Caldwell-Luc, where needed) 86 per cent showed improvements. No external operations were done. They say that striking results should not be expected too soon after the operation, but increasing improvement occurs with the passage of time.

Göbell says[117] he has been doing double sympathectomy and vagus section in severe asthmatic patients since 1923. He has operated on 110 with a mortality of 5 per cent. Since 1930, because of better selection of patients, two-stage operation, and local anesthetic, there have been no deaths. Various combinations of nerve operations have been tried, but he has found that bilateral sympathectomy combined with vagus section has yielded the best results. More than 60 per cent were cured or improved.

Levin[118] admits that results may be obtained by nerve operations in asthma but says that a better method is alcohol injection. The rami are accessible for neurolysis or neurectomy immediately below the points of junction with the intercostal nerves; the trunk can be reached above the level of the neck of the fourth rib. In a series of 23 patients treated by alcohol injection, 75 per cent obtained complete relief and the others were partially relieved.

Symptomatic.—Using a 1:1000 adrenalin solution, Lageder experimented with the effects of its inhalation in 18 cases of asthma.[119] Increase in residual air and decrease in vital capacity were the findings before treatment. After inhalation of adrenalin the vital capacity was increased in those who were relieved. In the others no change took place. The inhalations had no effect on the blood pressure or the blood sugar. The following year Welzer[120] mentions again inhalation therapy with adrenalin but discusses chiefly inhalation treatment with a preparation containing papaverine, eumydrin, adrenalin, hypophysin, and nitrite.

Graeser and Rowe[121] experimented further with this form of symptomatic treatment. By using a more concentrated adrenalin (1:100) they improved their results. In a series of 40 asthmatic patients the atomization of this solution, with a special apparatus which gave a fine spray, produced relief practically uniformly. The added advantage over the hypodermic administration of this drug lies in the fact that practically no by-effects, such as tachycardia, nervousness, insomnia or pallor, are produced. Since these authors read their paper, I have had sufficient experience with this method to confirm their findings in the main. My results, however, are not quite so striking.

Some patients fail to obtain any relief; some are relieved for only a few minutes; and in any patient, if the attack is very severe, this treatment is apparently insufficient. When the asthma is only part of a general allergic reaction, such as in a systemic reaction following specific therapy or in a food allergy, this method is not to be expected to yield results. Maetzger[122] reports findings similar to those of Graeser and Rowe.

It is claimed by Koschade[123] that asthma may be relieved by percutaneous administrations of the medication (hypophysin) by means of ointments rubbed into the skin. In experiments with pseudoephedrine Bray and Witts[124] found that it was more effective than ephedrine in lessening the frequency of attacks of asthma in children, but it was less efficient in relieving the actual attacks in adults. Valentine and Fitzgerald[125] describe several cases of acute urinary retention due to ephedrine in elderly male asthmatic patients.

In four patients with continuous asthma Cohen and Rudolph[126] administered adrenal cortical extract with no appreciable effect. The Pottengers[127] also discuss cortical extract. They obtained good results in asthma with the latter, especially when epinephrine by mouth was added to the treatment. They found that the oral administration of sodium chloride—3 to 6 gm. in 8 ounces of water one-half hour before meals—was also helpful.

Because it had been shown experimentally that strychnine stimulation of the adrenal gland resulted in an increase in adrenalin output greater than the dose usually given for relief of asthmatic attacks, Cohen and Rudolph[128] tried the therapeutic effect of strychnine. Partial relief was obtained at times, but the good results were overshadowed by the complicating hypertonicity.

Faragó finds[129] that through the inhalation of 8 per cent carbon dioxide mixed with oxygen a portion of asthmatic attacks can be favorably influenced. Usually he treated his patients daily for fifteen to twenty minutes. As a result of the inhalation there is a diminution of the alkali reserve, an increase in the acidity of the blood and milk and an unaltered pH of the urine.

Special Methods.—Attention has already been called to a number of favorable expressions regarding the use of stock and autogenous vaccines in asthma.[94-97, 114] The successful employment of pertussis vaccine has also been mentioned.[98, 99]

Balyeat and his coworkers[130] believe that most cases of asthma have a dual cause, the specific factor and a mechanical factor produced by tenacious or purulent mucus. Iodized oil intratracheally is described as an ideal means of treating the mechanical cause. From 5 c.c. to 10 c.c. of the oil is instilled at weekly, biweekly, or monthly intervals. Of 50 patients with asthma in whom poor results were obtained by

allergic management alone, good results were obtained in 35 by the addition of the iodized oil to the regular treatment. A similar effect seems to be accomplished by Shambaugh and Alter[131] by postural drainage. The patient kneels on a chair and places both hands on the floor, giving the thorax as nearly a vertical position as possible. He then coughs repeatedly. The position is maintained for at least three minutes, regardless of the amount of exudate produced. This is done twice daily. The procedure is used for prevention of paroxysms. They warn that underlying causes must also be treated. Bronchoscopic drainage is again recommended.[132]

One of the most novel and ingenious methods of treating status asthmaticus is described by Barach.[133] The author says that the dyspnea of asthma is due to neither anoxemia nor carbon dioxide excess, but rather to an interference with the habitual rate of filling and emptying of the lungs. The increased effort required to obtain the normal velocity of air delivered to and from the lungs appears to give the sensation of dyspnea and represents an equilibrium that functions to a degree independently of the respiratory gaseous exchange. He reasoned that if the column of respired air could be made more easily movable some improvement might result. Since helium is one-seventh the specific gravity of nitrogen it was shown that a mixture of 80 per cent helium and 20 per cent oxygen caused a saving of 34 per cent to 50 per cent respiratory effort. By a special closed apparatus such a mixture was administered to several desperate cases of status asthmaticus. Usually after 6 to 10 inspirations there was definite improvement. By this therapy an adrenalin-fast individual was made to respond to this drug. The author definitely states that the acute attacks of asthma are not aborted by the helium oxygen mixture.

Several rather conflicting reports concern the effect on glycemia. In several patients, Wegierko[134] found that the production of a hypoglycemia by insulin resulted in the relief of the asthmatic attacks. The report of Eisenberg,[135] that he obtained good results in asthma by fasting, might also be cited as corroborative evidence by some for the beneficial effect of hypoglycemia. On the other hand, the finding of a slightly decreased blood sugar in asthma as reported by one author[6] and the infrequency of association of asthma and diabetes[15] would tend to contradict the views of Wegierko. More conflicting papers deal with the beneficial effect of administering glucose. Shillito[136] cites a case in which the administration of insulin caused severe asthma by the production of hypoglycemia. Intravenous glucose solution, from 50 c.c. to 100 c.c. of 50 per cent solution, was found by Lepak[137] to be of distinct help in severe attacks of chronic asthma. The author regards the action of the glucose as probably due to the changes in osmotic pressure and the removal of fluids from the tissues. In the

management of intractable asthma, Wilson[138] recommends the use of two to four liters of glucose intravenously at the rate of 500 c.c. per hour, the optimum concentration of the glucose to be 10 per cent. In addition he recommends a change of environment, preferably to an allergen free room in a hospital, and the use of chloral hydrate and bromide by rectum. He warns strongly against the use of morphine.

The value of breathing exercises in asthma is stressed by Livingstone and Gillespie.[139] Exercises are taken daily for at least ten minutes each time. The patients are taught to take a short inspiration through the nose followed by a long expiration through the mouth. The aims of these exercises are: to empty the lungs more completely; to reeducate the automatic diaphragmatic movements and to diminish the thoracic type of breathing; to relax spasmodically contracted muscles; and to mobilize the ribs and chest wall to prevent kyphosis. In 52 out of 75 patients treated in this manner, definite improvement was noted. Weltz[45] also recommends respiratory exercises and gymnastics. Respiratory exercise, massage and kneading of muscles of the abdomen and back are recommended by Kirchberg.[140]

With surgical ether anesthesia Kahn[141] was able to break the habit spasm in several instances of asthma so that the asthma was made much lighter for a period of several weeks. This differs from previous use of ether for asthma in that it was not used during status asthmaticus, but in the free period. He describes its use in four pollen asthmatic patients.

Miranda Gallino[142] reports on roentgen treatment of 196 cases of asthma with 31 per cent cured, 50 per cent improved, and 19 per cent failures. His technic is as follows: 170 KV, 4 MA, F.D. 40 cm., filter 0.5 mm. copper and 1 mm. aluminum. Spleen fields 10 × 15 cm. with 480 international r units and thoracic fields 20 × 24 cm. with 320 r units are employed. One irradiation is given over the spleen, one over the anterior thorax, and one on the posterior with an interval of forty-eight hours between exposures. This series is repeated every four weeks; if there is no improvement after three series, the procedure is abandoned. If there is improvement, the irradiation is usually continued over the thorax only every four to six weeks. If the attacks are very intense, frequent and prolonged, the doses are fractioned.

Landsman[143] suggests that the commonly observed effects of weather changes and climate on asthma may be due to changes in the ionization of the air. For that reason he tried the effect of ionized air inhalations in a series of 79 asthmatic patients, using chiefly negatively charged ions. The latter were conducted from a static machine into two glass chambers and thence through a tin funnel into the tube of a gas mask worn by the patient. Treatments were given from ten to forty-five minutes daily for 30 times. In 64 cases improvement was produced.

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185 NORTH WABASH AVENUE

Selected Abstracts

Asthma

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

The Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larnyx and Trachea. Barach, A. L.: Ann. Int. Med. **9**: 739, 1935.

Helium has a specific gravity of one-seventh that of nitrogen and a mixture of 80 per cent helium with 20 per cent oxygen is one-third the weight of the same volume of air. Since the pressure required to move an object is proportional to its weight, it was assumed by the author that such a light gas mixture could be breathed with less effort in conditions in which difficulty in ventilating the lungs was present. By actual test it was shown that such a mixture demonstrates a saving of 25 to 50 per cent of respiratory effort.

The author describes four patients ranging in age from twenty-two to fifty-two years, who were seen in status asthmaticus. One of them was apparently dying. Three of them were adrenalin fast. Inhalation of helium-oxygen mixtures produced improvement in all, usually after the first 6 to 10 inhalations. As a result of the treatment the muscles relax, the breathing becomes more free, and the color improves. Usually after one hour of such treatment the patient is free from asthma for six to eight hours. More prolonged treatment increases the interval of freedom. When large sonorous râles are present (involvement of large bronchi) relief is more easily obtained than when fine piping râles are heard. One of the outstanding results of this treatment is the loss of refractoriness to adrenalin, so that when attacks do occur adrenalin is capable of giving the customary relief. The refractoriness to adrenalin in status asthmaticus is explained on the basis of fatigue, increased alveolar distention, and fatigue of the sympathetic nervous system. In acute asthmatic seizures helium inhalation was not found to be effective, nor could such attack be aborted in this manner.

The dyspnea of asthma is described by the author as due neither to anoxemia nor to carbon dioxide excess, but rather to an interference with the habitual rate of filling and emptying of the lungs. He says that the increased effort required to obtain the normal velocity of air delivered to and from the lungs appears to give the sensation of

dyspnea and represents an equilibrium that functions to a degree independently of the respiratory gaseous exchange.

Graphic records of the pulmonary ventilation in a patient with continuous asthma receiving helium-oxygen mixtures showed: (1) decrease in pulmonary ventilation; (2) decrease in pulmonary pressure; (3) relative and absolute diminution in the length of the expiration; and (4) increased rest period between respiratory cycles.

Other types of cases of severe obstructive dyspnea are mentioned in which the helium was of benefit. Because of the marked anoxemia in these cases a higher percentage of oxygen was needed.

An interesting experiment is cited in the case of a sixty-year-old man with emphysema, chronic nephritis, myocardial fibrosis, paroxysmal cardiac dyspnea, and Cheyne-Stokes breathing. Helium-oxygen mixture improved the condition somewhat, because of the lesser difficulty in breathing and greater diffusion of the oxygen. When 100 per cent oxygen was inhaled, the breathing became entirely regular, demonstrating the chemical factor in the causation of this type of cardiac dyspnea.

In the technic of administration of helium-oxygen mixtures a number of points are of importance. Helium is noninflammable and nontoxic. It is very costly, however, and because of its very great diffusibility special precautions are taken against leaks and losses. The gas is usually administered with the oxygen through a special closed apparatus or by means of a tent. The concentration of helium must be watched. The concentration of oxygen must be constantly watched, since there is real danger from asphyxia. Many devices are suggested to safeguard the deprivation of oxygen—air analysis, emergency automatic tanks, and alarm signals.

The Treatment of Bronchial Asthma by Dorsal Sympathectomy; Direct and Indirect (Use of Alcohol). Levin, G. L. L.: Ann. Surg. **102**: 161, 1935.

There is sufficient pathologic and clinical evidence to show that the dorsal sympathetic nerves, especially the second to the sixth rami, contain both contractor and sensory fibers to the bronchial musculature. The rami are accessible for neurectomy or for neurolysis by absolute alcohol, immediately below the points of junction with the intercostal nerves; the trunk can be reached above the level of the neck of the fourth rib. He reviews the other methods of vagus and sympathetic operations and concludes that from the clinical and surgical evidence the vagus is not the constrictor bronchial nerve.

The methods recommended are either the destruction of the rami by several injections of alcohol, 2.5 c.c. at a dose, or by a similar destruction of the upper portion of the thoracic ganglionated trunk. Of 23

patients with severe asthma treated by these methods complete relief was obtained in 75 per cent with varying degrees of improvement in the remainder. Perforation of the pleura took place in three patients with no serious consequences.

Bronchial Asthma Due to Paper Sensitivity; Case. Bennett, T.: New England J. Med. **213**: 121, 1935.

In a ten-year-old girl who had asthma of six years' duration it became apparent that the attacks followed shortly the eating of paper, a habit which had persisted since infancy. The author obtained a marked reaction from a skin test with paper. Psychoanalytic treatment broke the child of the habit, and she has not had any asthma for several months.

Concurrence of Diabetes Mellitus and Bronchial Asthma. König, F.: Med. Klin. **31**: 545, 1935.

Among 1,240 diabetic patients the author encountered only three instances of asthma. He cites other reports which indicate that among asthmatic persons there are few diabetics (6 in 4,000). The explanation offered for the rarity of association between these two diseases is that there is an antagonism existing between insulin and adrenalin.

The Diagnostic and Therapeutic Use of Iodized Oil in Cases of Intractable Asthma. Balyeat, A., Seyler, L. E., and Shoemaker, H. A.: Radiology **24**: 303, 1935.

The authors believe that most cases of asthma have a dual cause, a specific factor and a mechanical factor—the latter produced by tenacious or purulent mucus. They say that attention should also be given to the mechanical causes. Iodized oil intratracheally is described as an ideal means of treating the latter. From 5 c.c. to 10 c.c. of the oil is instilled at weekly, biweekly, or monthly intervals. Of 50 patients with asthma in whom poor results were obtained by allergic management, good results were finally obtained in 35 by the addition of the iodized oil treatment.

Ionized Air in Bronchial Asthma. Landsman, I. E.: Sovet. vrach. gaz., pp. 227-232 (Feb. 15), 1935.

The author calls attention to the literature dealing with effects of weather on the human and animal organism. He thinks that the degree and polarity of ionization is the determining factor in this effect. He believes also that that constitutes the probable reason why asthmatic patients are often relieved by a change of climate.

Ionized air inhalations were tried in 79 cases of bronchial asthma. In the majority (63) negatively charged ions were used because they were found to have more beneficial effect on the neuropsychic tonus than positively charged ions. The ions were conducted from a static machine of Mersedes type into two glass chambers 70 cm. × 70 cm. and thence through a tin funnel into the tube of a gas mask worn by the patient. The first treatment for adults was of twenty minutes' duration and was increased each day by five minutes up to forty minutes. For children the beginning and maximum treatments were fifteen and twenty-five minutes. A course constituted 30 treatments.

In 64 patients (81.5 per cent) the treatments produced improvement. Children from eight to twelve years of age were especially benefited. The following results were evident: improved breathing, more even pulse, changes in morphologic composition of blood, decrease in eosinophilia and lymphocytosis, increase in hemoglobin, slowing of sedimentation rate, change in character of sputum, and disappearance of Charcot-Leyden crystals and Curschmann spirals. The author says that this treatment is contraindicated in cardiac asthma.

Asthma in Maladjusted Children. Freudenberg, S.: Fortschr. d. Med. **53**: 392, 1935.

Among asthmatic children one may frequently observe those with a marked inferiority complex and a desire for recognition and attention. The author reports the case of a boy of eleven years who had had asthma since he was three years old. He was sent to a health resort where he was free from attacks, but relapsed as soon as he was home. His asthma became much worse after the birth of a sister. Evidently he used his attacks as a means of centering his mother's attention on himself.

In a second case, a girl of eight years, the desire to excel her older brothers and sisters held her in a breathless state of tension. Asthma attacks are a suitable form of expression of such a state. In this case there was also a predisposition to asthma. Her father and her oldest brother were asthmatic.

In both cases, the author states, a gradual encouragement and the arousing of self-confidence are indispensable conditions before a cure can be accomplished. Change of environment is often the best means to this end.

Mold Allergy: Its Importance in Asthma and Hay Fever. Feinberg, S. M.: Wisconsin M. J. **34**: 254, 1935.

Attention is called to the important rôle played by fungi in the direct or complicating causation of bronchial and nasal allergy. Of 243 patients with respiratory allergy 68 gave positive cutaneous reactions

to one or more of several fungi. The greatest source of this mold sensitization is the air-borne spores. The author makes the point that reactions to fungi are not rare or unusual. These allergens should not be regarded as possible sources of trouble under exceptional environments but rather as sources of continuous exposure due to their constant presence in the atmosphere.

Hay Fever

UNDER THE DIRECTION OF W. C. SPAIN, M.D., NEW YORK CITY

Coseasonal Hay Fever Therapy With Special Reference to Low Pollen Doses. Rinkel, Herbert J.: Clin. Med. & Surg. **42**: 426, 1935.

Following the work of Vaughan in treating hay fever patients with low seasonal dosage, Rinkel states that low coseasonal doses up to 200 to 400 units will protect the average seasonal patient. If such dosage levels do not, his advice is to look elsewhere for the cause of symptoms. The author describes six such cases of patients sensitive to pollens, inhalants and foods. Charts for each patient, maintained daily, containing curves of symptoms, foods ingested, and the pollen content of the air, enabled the author to trace symptoms to other causes than to insufficient pollen treatment.

In several hay fever cases with an unsatisfactory result, when the patients were given as maximum dosage 2,000 to 4,000 units preseasonally, they improved the following year upon a maximum of 300 to 400 units seasonally, when proper attention was given to food elimination.

Food sensitiveness was suspected by daily variations of symptoms against a known pollen curve (daily) in the presence of an apparently sufficient dosage which rarely exceeded 400 units. Depending upon the severity of symptoms in different cases, treatments were given at intervals of from twenty-four hours to several days. The offending foods were replaced after frost, with no return of symptoms.

As a result of his study these conclusions were drawn. (1) Persons sensitive to pollens only, were easily and always relieved of symptoms. (2) In persons sensitive to excitants other than pollens, results of pollen therapy depend as much on complete and successful treatment of the concomitant excitants as upon correct pollen doses. (3) Variations in the symptom curve do not closely follow the curve of the pollen count. (4) No patient receiving a dose of 400 units obtained better results by increasing that dose. (5) Persons with accurate treatment of their complicating excitants gave better results with small pollen doses than previously with larger doses, when the complicating excitants were ignored.

Disappointing Results From the Ionization Treatment for Hay Fever. Ramirez, M. A.: J. A. M. A. **106**: 281, 1935.

In 50 cases of true seasonal hay fever Ramirez employed the Warwick method of intranasal ionization, following the procedure in every detail. In the first group the patients were given the Warwick ionization treatment before the expected date of pollination. One week later they were tested by permitting inhalation through the nose of a very small amount of pollen, to which a positive skin test had previously been obtained. All had severe symptoms of hay fever immediately.

In the second group of true hay fever cases the ionization treatment was given as in the first group, before the date of pollination, but the inhalation test was performed two weeks later. All had severe symptoms immediately.

In the third group the ionization procedure was identical with that used in the first and second groups, but instead of testing the effect by inhalation of the pollen, the patients were allowed to go without further treatment in order to observe whether or not they would have symptoms as in previous years upon the appearance of pollen in the air. Every patient showed symptoms of hay fever as soon as the season started, identically as in previous years when no treatment had been given.

In a fourth group of the pollen cases the patients were treated by the ionization method during the season while suffering from acute symptoms. In no case was there any relief.

In contrast, 25 patients with nonspecific, perennial vasomotor rhinitis appeared benefited, in the majority of cases, by the ionization procedure.

The author concludes that the intranasal ionization treatment for hay fever has no merit; while for nonspecific, perennial vasomotor rhinitis it seems to be of benefit.

Notes on Pollinosis in Lombardia During the Last Three Years. Sangiorgi, P.: I Quaderni Dell' Allergia **1**: 173, 1935.

A general discussion is given by the author, of the clinical forms of hay fever seen by him in his practice. In addition to describing the usual varieties, including types with asthma and with dermatitis as complications, Sangiorgi states that very often pollen hypersensitiveness involves many other organs and systems of the body. Among the results of pollen irritation are: flatulence, colic, constipation; neuralgia of the trigeminal nerve, especially of the infraorbital branch; vertigo; menstrual irregularities; inflammation of the genitals; deafness; and diminution in the senses of smell and taste.

The author considers of importance the fact that during the period of hypersensitiveness to pollens, immunity to staphylococcic and streptococcic infections increases, whereas tolerance to alcohol decreases. He feels that even when due allowance is made for the increasing ability to recognize hay fever conditions, there is still a rapidly growing number of hay fever patients. He feels that our modern civilization, particularly of the cities, is responsible for the disturbance in the vegetative nervous system, upsetting its equilibrium and thus predisposing our constitutional habitus toward allergic diseases. People living in the city are described as being more affected by hay fever than those living in the rural districts. Intellectual and physical overwork imposed upon the inhabitants of cities is considered to exercise a great influence in the number of hay fever cases.

From an analysis of his hay fever patients the author has found that professional people (physicians, lawyers, teachers, etc.) account for 55 per cent of the total; artists (sculptors, painters, etc.) 13 per cent; industrialists, clerks, working people, each 10 per cent; farmers, 2 per cent.

The author concludes that it is likely that in the determination of pollinosis, besides the peculiar constitution of the person on the one side, and the allergenic power of the pollens on the other, there exist other factors, perhaps meteorological or local, which may clear up many points, apparently obscure, in the etiology and pathogenesis of pollinosis.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

Oral Immunization to Colds. Rockwell, G. E., Van Kirk, H. C., and Powell, H. M.: J. Immunol. **28**: 475, 1935.

The authors studied the immunizing properties of vaccines, orally administered, on the incidence of colds. Five hundred subjects were treated. They consisted of five groups: nurses, life insurance company employees, machine shop workers, medical students, and a general group. As controls 536 other subjects taken from the same groups were studied. The vaccine consisted of single strains of pneumococcus and streptococcus organisms which are high in bile-resisting heterophile antigen content. Dosage was administered in capsules containing, in dry form, 100 billion of each organism. One capsule was taken before breakfast on seven consecutive mornings and then one a week for the remainder of the "cold" season.

Among the treated cases, 38 with a previous history of almost continuous colds experienced only 1.08 colds per person during the year of treatment. Of nine similar cases among the controls, eight reported

the same frequency of colds as in previous years. Four hundred and sixty-two persons with a previous average of 3.03 colds per person per year, experienced only 1.30 colds per person during the year of treatment, a decrease of 57 per cent. During the same period the average of the similar control group fell from 2.49 to 2.19 colds per person, a diminution of only 12 per cent.

The Relation of Heterophile Immunity to the Incidence of Colds. Rockwell, G. E., and Van Kirk, H. C.: J. Immunol. **28**: 485, 1935.

Thirty subjects who received oral vaccine as described above and 17 controls were studied in detail to determine the response of each individual to the feeding of the heterophile antigen and its relation to the incidence of colds. The patient's serum was titrated at intervals to determine its content of hemolysin (heterophile antibody) for sheep corpuscles. This was expressed in terms of heterophile units. It was found that those patients who responded most to the antigen were almost free of colds, while those who failed to produce the heterophile antibody suffered about as many colds as in previous years. In 11 tested subjects, whose serum contained 150 to 600 heterophile units per c.c., the incidence of colds for the year fell 96.7 per cent. In six tested persons with serum containing 60 to 75 heterophile units per c.c., there was a decrease of 76.1 per cent in the incidence of colds. In 13 treated patients with less than 60 heterophile units per c.c., the average incidence of colds actually rose 6 per cent over the average of previous years. Among the 17 untreated subjects, all but three lacked heterophile antibodies. Two of the latter had a titer of 600 units and had experienced no colds during the year.

A Study of the Effects of Vaccine Injections Upon Skin Sensitivity. Touart, M. D., Thomas, W. S., and Tucker, W. L.: J. Lab. & Clin. Med. **21**: 365, 1935.

The writers studied the influence of vaccine therapy upon the reactions obtained by intracutaneous testing with these materials. Tests were made with about 0.01 c.c. of a 10 per cent volumetric suspension of killed bacteria in normal saline solution and 0.25 per cent tricresol. The immediate and delayed reactions were separately recorded, according to the authors' own methods of tabulation.

Thirty-three patients suffering with allergic symptoms associated with infection were studied. Complete bacteriologic surveys were made of all accessible foci of infection, abnormal discharges, and, in some cases, the feces. A standardized vaccine was made of each organism. Intracutaneous tests with these vaccines were made and repeated after the completion of a series of treatments with those organ-

isms which gave positive reactions. Treatment varied from three months to three years in duration. Injections were given intracutaneously or just beneath the skin. The 33 cases consisted of 5 cases of allergic coryza, 20 of asthma, and 7 of chronic arthritis. The vaccines used in treatment included various types of streptococci, staphylococci, *B. coli, Micrococcus catarrhalis,* and others.

One hundred and six vaccines were used for treatment in the 33 cases. Comparative skin tests done before and after treatment disclosed the following results: The immediate reactions were unchanged in 67.0 per cent, decreased in 23.0 per cent, and increased in 10.0 per cent; the delayed reactions were unchanged in 17.9 per cent, decreased in 72.6 per cent, and increased in 9.5 per cent.

Similar comparative skin tests with 62 vaccines not employed in the treatment of these cases yielded the following results: Immediate reactions were unchanged in 74.2 per cent, decreased in 12.9 per cent, and increased in 12.9 per cent; delayed reactions were unchanged in 38.7 per cent, decreased in 40.4 per cent, and increased in 20.9 per cent. Hence, although the immediate reactions seemed uninfluenced by treatment, the delayed reactions were definitely diminished. The reduction, the writers believe, was proportionate to the degree of clinical improvement of the patient at the time of the retest. Patients with marked improvement showed a diminution of 85.1 per cent in their delayed reactions, those moderately improved 66.6 per cent, and the unimproved 38.1 per cent.

Similar tests with vaccines not employed in treatment showed a decrease of 46.3 per cent in the delayed reactions of the markedly improved patients, 40.0 per cent in the moderately improved, and 18.2 per cent in the unimproved. For this reason, the writers believe that the delayed skin reaction with vaccine not only is useful in selecting the proper vaccine for treatment but may also be used as an indicator of the progress of desensitization.

Skin Reactions to Products of Hemolytic Streptococcus. Gibson, H. J., and Thomson, W. A. R.: Arch. Dis. Child. **10**: 429, 1935.

The authors studied cutaneous allergy to the hemolytic streptococcus and its relation to the Dick reaction in a series of 586 individuals. Two-tenths c.c. of an extract of ground-up streptococci in 0.5 per cent carbol-saline was injected intracutaneously as the test dose. The hemolytic streptococcus had been obtained from the throat of a rheumatic patient and was a typical strain of *S. pyogenes.* Readings were made in twenty-four and forty-eight hours.

Positive reactions to hemolytic streptococcus extract were found to increase in frequency up to the tenth to fourteenth year and then to

remain fairly constant. Positive reactions during the winter months (October to March inclusive) occurred in 84 per cent of cases as compared to 64.5 per cent of cases during the summer months. The presence or absence of *Streptococcus hemolyticus* in the throat swab at the time of the test did not appear to influence the frequency or degree of the skin reaction. Reactions to hemolytic streptococcus extract occurred with almost equal frequency among Dick-positive and Dick-negative cases. Repetition of the tests with hemolytic streptococcus extract and Dick toxin on the same individual at intervals of from two to four weeks revealed a marked variation in results with both substances, which could not be correlated with the clinical condition of the patient nor the presence of hemolytic streptococcus in the throat swab. The writers believe that analogous variations in delayed cutaneous reactions could be obtained with the repeated intracutaneous injections of horse serum.

Intramuscular injections of hemolytic streptococcus extract did not produce local, focal, or general reactions, nor did they materially influence the cutaneous reactions. The sera of rabbits immunized with hemolytic streptococcus extract were able to neutralize the substance inducing the cutaneous reactions in about one-half of the cases tested. The skin reacting principle was found to be markedly thermostable.

A Study of the Pneumococcus Toxins. Coca, A. F. (with the assistance of Henry W. Straus and Ella F. Grove): J. Immunol. **30**: 1, 1936.

By growing pneumococci in an atmosphere containing from 15 per cent to 20 per cent of carbon dioxide the author was able to obtain in the filtrates of this culture a toxin with high antigenic powers for the stimulation of antitoxin in human beings. The filtrates of cultures grown under ordinary atmospheric conditions lacked this property.

The subcutaneous injection of this toxin in 34 children between the ages of two and one-half and three and one-half years produced a temperature of from 101° to 105° in all but two, who gave previous histories of bronchopneumonia and severe bronchitis. This pyrogenic activity of the toxin could be destroyed by neutralization with the serum of pneumonia (type I) convalescents in two cases. A single dose of toxin often induced immunity, and about two-thirds of the susceptible children became immune within two weeks after a second injection.

Skin tests with the toxin were performed by the intracutaneous injection into the upper arm of 0.1 c.c. of the filtrate in various dilutions. Susceptibility of the host manifested itself by the presence of erythema and edema at the site of the test at a twenty-four hour reading. Thirty-one patients suffering from or convalescing from pneumococcus pneumonia responded negatively to skin tests with type I toxin filtrate.

Parallel cutaneous tests in the same person with toxin filtrates of pneumococcus types I, II, III, and VII, gave evidence suggesting type-specificity among them. The author was also able to immunize eight susceptible individuals by injection of type I toxin so that their cutaneous susceptibility to this filtrate diminished or disappeared while their positive reactions to the filtrates of types II, III, and VII remained unaffected.

All attempts to demonstrate neutralization of toxin in toxin-antitoxin mixtures by skin tests with these mixtures on susceptible subjects were unsuccessful. Positive reactions resulted under all circumstances, even with mixtures which produced no temperatures when injected subcutaneously into susceptible children. These results indicated that in susceptible skins, the toxin in the toxin-antitoxin combination was liberated from the union in amounts sufficient to exercise its local toxic effect.

The detoxification of pneumococcus I toxin with formalin seriously impaired its antigenic properties. The rubbing of concentrated toxin into the skin failed to induce immunity in a series of eight subjects.

The skin test dose of the pneumococcus type I toxin is about 0.025 the pyrogenic dose. (The skin test dose of most streptococci is about .001 the pyrogenic dose.)

Destruction of the specific polysaccharide in type III toxin filtrate did not influence its toxicity at all, thus indicating that the toxin is not the type-specific polysaccharide.

Tuberculin Allergy in Acute Infectious Diseases: A Study of the Intracutaneous Test. Westwater, J. S.: Quart. J. Med. N.S. **4**: 203, 1935.

Mantoux tests were performed on about two thousand cases of acute infectious diseases including measles, scarlet fever, chickenpox, diphtheria, and pertussis. About 0.1 c.c. of a mixture of human and bovine O.T. in a dilution of 1:1,000 was injected. Tests were performed usually on admission to the hospital and at varying intervals of from one to several weeks thereafter. Frequent repetition of tests on the same patient was avoided.

The Mantoux reaction was most severely influenced by the rashes of measles and scarlet fever. In about one-half the cases sensitive to tuberculin, negative reactions resulted from the Mantoux test when this was performed during the exanthematous stages of these illnesses. This period of hyposensitivity occurred most frequently during the first week after the appearance of the rash and occasionally persisted into the following week. This suppression of reactivity may be responsible for a late reaction, i.e., one which appears four or more days after testing, usually after the height of the eruption has passed.

Refractoriness of the skin resulting from the rash is the most important factor in the failure to obtain positive Mantoux tests after the eruption has appeared. The prodromata of measles and scarlet fever, regardless of their severity, do not interfere with the tuberculin reaction. The more intense the rash, the greater is the depression of reactivity. In almost all instances, increasing the testing strength of the tuberculin to 1:100 did not overcome the diminished reactivity of the skin. Chickenpox, diphtheria, and whooping cough do not appreciably affect the tuberculin reaction.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK CITY

Does the Result of the Patch Test According to Jadassohn-Bloch Show Dependence Upon Fever and Skin-Sweat? Mahler, Walter: Münster i.W. u. Düsseldorf: Diss. 1934.

Mahler examined the question as to whether the result of the patch test in eczema could be influenced by nonspecific factors. He tested the regional differences of the skin and discovered that reactions on the flexor surfaces of extremities were somewhat stronger than those on the extensors; furthermore, that the upper half of the body (above navel) showed stronger reactions than the lower half. Above all, Mahler experimented to determine whether fever and increased sweating could influence reactions. Fifty patients with high fever were tested with 14 different substances; tests were made during fever attacks and afterward; and in 24 pneumonia cases, a third test was made during increased sweating at the crisis. In general, patients with high fever showed clearly a nonspecific increase in skin reactivity; but none (excepting one reaction to 50 per cent turpentine salve) showed a reaction resembling that of a specific hypersensitivity. Strong sweating at normal body temperature did not affect results of patch testing. There is thus no danger that skin tests, which must frequently be performed on persons exerting themselves and sweating (for compensation cases, etc.), will be influenced to any extent by the increased sweat production.

Urticaria, Edema and Purpura Following Small Doses of Di-nitrophenol. Report of a Case. Noun, Maurice Henry: Arch. Dermat. **32**: 288, 1935.

Di-nitrophenol is given internally as an anti-obesity cure. It strongly stimulates the metabolism. In predisposed persons it leads to unpleasant after-effects. Icterus, agranulocytic angina, urticaria and maculo-

papular exanthems have been observed. Even some fatal cases have been described. Noun gave a forty-year-old, otherwise healthy man of 240 pounds, di-nitrophenol twice daily in doses of 0.13 gm. (half of the usual dose). About three weeks after the beginning of this treatment, a severe urticaria with purpura developed. This condition rapidly improved after epinephrine, diet, baths, and magnesium sulphate. Skin tests and blood-antibody experiments could not be undertaken.

Allergic Purpura. Eyermann, Charles H.: Southern M. J. **28**: 341, 1935.

Of 18 patients in whom purpura followed deliberate ingestion of food, 5 had positive family histories for allergy, and 10 gave positive skin tests (of which 6 indicated the offending food). Purpura more often followed the eating of egg, milk, wheat, chocolate, beef, etc., in that order of frequency.

In most instances, purpura of allergic origin due to food is identified by the occurrence of allergic phenomena in the antecedents; and, in the patients, by eosinophilia and positive skin tests. Additional help in diagnosis may be obtained from the character of past or present skin lesions and from the history of past or present visceral crises and joint pains. The accumulating evidence indicates that allergy will explain a great number of cases classified as Schönlein-Henoch's purpura, or the erythema group of diseases with visceral manifestations.

Three cases are reported, which have been observed for several years.

Results of Patch Tests With Gold Sodium Thiosulphate. Lichtenstein, Meyer R., and Stillians, A. W.: Arch. Dermat. **31**: 758, 1935.

A young man with pulmonary tuberculosis was given 6 intravenous injections of gold sodium thiosulphate, maximum dose 0.25 gm. This series of injections was followed by an exfoliative dermatitis persisting several months. A patch test with 33 per cent gold sodium thiosulphate in wool fat produced a positive vesicular reaction. Control tests with other gold salts, etc., were all negative. In over 100 patients who showed some skin manifestations after gold treatment, patch tests with gold sodium thiosulphate were always positive, and other tests always negative. Some patients showed a positive skin reaction even before a dermatitis broke out. In the discussion, Obermayer says that the gold ammonium salt, introduced by himself and Kharasch, seems to be less toxic than the thiosulphate as shown by the experiments of Lichtenstein. Even larger doses are well tolerated, and the therapeutic results seem as good as those of the other gold salts. Becker and Mitchell emphasize that one must be very careful in the evaluation of these skin tests.

Allergy and Skin Reactions to Gold. Giauni, Gino: Boll. d. Ist. sieroterap. milanise **14**: 297, 1935.

Giauni observed 19 cases treated with gold preparations, which showed erythemas or drug emphasis from gold. After eruption each patient was tested with 1 per cent solution of the medicaments employed. Cutireactions (intracutaneous test): 6 positives of 8 erythemas, 2 positives of 3 so-called nine-day erythemas, 1 positive in 1 gold reaction resembling seborrheic eczema, 2 positives in 3 universal erythrodermas, 3 positives in 4 urticarial pruritus. Epidermal reactions (patch tests) (results in groups as above): 5 of 8, 2 of 3, 1 of 1, 2 of 3, and 2 of 4. Intradermo-reactions were positive in 13 out of 19 cases. Königstein-Urbach and Prausnitz-Küstner reactions were negative in all 19 cases, presumably because of the used antigens. The gold reactions are not to be considered as poisonings, but as expressions of individual constitutions which demand a change of therapy.

Concerning the Specific Sensitivity of the Skin to Simple Chemical Substances. Wedroff, N. S., and Dolgoff, A. P.: Arch. f. Dermat. **171**: 647, 1935.

After a review of results with experimental sensitization of human beings and of mass sensitizations (occupational), detailed results are given of sensitization experiments with di-nitrochlorbenzol in acetone in 72 patients with eczema and in 20 persons with healthy skin. Fifty eczema patients were specifically sensitized by one application of drops of 0.03 c.c. 10 per cent di-nitrochlorbenzol. The incubation period varied from eight to twenty-four days. The sensitivity increased to more than 100,000 times the original degree; and spontaneous retrogression of sensitivity took from two to three hundred and sixty days. Eczema patients were more readily sensitized than normal persons. Normal persons required up to 0.3 c.c. of a 30 per cent solution. Among the eczema patients, the tendency to develop a specific allergy fluctuated between negative and the very strongest tendency. Therefore not every eczema can be regarded as a hyperallergic reaction. Repeated applications on already sensitized individuals increased the degree and duration of the sensitivity. Existing eczemas did not exacerbate in the course of the experiment. Existing allergies to other substances (nickel) were not influenced in their course.

A Contribution to the Question of the Skin's Ability to React in "Chemical" Eczemas, Based on Experiments on Eczema Patients and on Healthy Persons With the Indicated Chemical Irritants. Wedroff, N. S., and Dolgoff, A. P.: Arch. f. Dermat. **171**: 641, 1935.

Wedroff and Dolgoff performed skin-function (patch) tests on 324 persons with skin disease and on 100 healthy test persons. They ap-

plied patch tests with petroleum, turpentine, arnica tincture, and 5 per cent formalin. It was found, as expected, that there was a higher degree of reactivity in the skin of the diseased persons. To determine more accurately the differences in reaction, the authors' perfected drop method was used with phenol in benzol, and with sublimate in acetone, in concentrations of from 3 per cent to 25 per cent on 150 eczema patients and healthy individuals. Eighty per cent of the eczema patients reacted to the 5 to 10 per cent solutions; 80 per cent of the healthy persons responded only to the 15 per cent to 20 per cent solutions. The question thus arises as to whether the nonspecific hypersensitivity of the majority of the eczema patients is not due to increased permeability of their skin.

Neurodermitis: Its Position in Relation to Eczema, and the Qualification for Its Designation. Stümpke, G.: Med. Klin. **19**: 1199, 1935.

This investigator attacks the concept which associates neurodermitis with eczema in view of the microscopic and, partly, the clinical picture, and brings out the differences which warrant the separation of these distinct entities. Eczema begins, as a rule, late in life. Infantile eczemas have many characteristics in common with neurodermitis, as Rost brought out in his differentiation between early and late exudative eczematoid. Eczema is due to a sensitization, often of long duration, and is cured by desensitization or by removal of the external irritant. Neurodermitis (eczematoid—Rost) extends, with interruptions, over long periods and can appear at any time of life. Itching is the primary manifestation in neurodermitis and leads secondarily to lichenification; whereas in eczema itching is the result of skin alterations. General treatment, notably arsenic therapy, is only exceptionally successful in eczema; whereas this is the principal method of treatment in neurodermitis. Among sufferers from eczema it is hardly possible to find a characteristic type. In neurodermitis, however, such a type can be pointed out—these patients suffer from vagotonia and frequently have strong hyperhydrosis, migraine, *ulcus ventriculi*, etc. The author explains neurodermitis as due to primary irritability of the nerve apparatus in the skin. Prognosis in neurodermitis is far less favorable than in eczema. Rost's nomenclature "eczematoid" does not sufficiently emphasize differences between neurodermitis and eczema. The designation "neurodermitis" is not quite satisfactory, as the importance of the rôle of the nervous system has not been absolutely proved. However, in view of constitutional considerations, neurodermitis must be differentiated from eczema; and this also leads to different therapeutic approaches in practice. [Neurodermitis here signifies our atopic dermatitis.]

A Few More Words About the Etiology of the Neurodermitis of Brocq, on Occasion of a Rare Case of This Dermatosis. Photinos, P.: Bull. Soc. Franç. Dermat. **42**: 982, 1935.

Photinos first mentions briefly his 10 typical cases of neurodermitis, some of which have persisted for decades. Efficacious treatment consists of 1 per cent iodin-alcohol with cold cream. There follows a more detailed description of a typical neurodermitis on the neck. It is interesting that here the agent of erythrasma—*Microsporon minutissimum*—was found. This case is important because of the occurrence of this fungus on the neck, and because of its being found in a disease clinically to be called neurodermitis. The author claims that this is a neurodermitis Brocq elicited by a microorganism.

Concerning Radiation Therapy of Eczemas and of Dermatoses Similar to Eczemas in Children. Tachau, P.: Klin. Wchnschr. **14**: 647, 1935.

In common eczema, neurodermitis, and seborrheic eczema, particularly when localized on the face or scalp, roentgen rays are unquestionably therapeutically superior to other rays. The author gives infants 3 to 4 treatments of 30 r. under 0.5 mm. aluminum at intervals of ten days. Children over three years get 50 r.; and over seven years, 80 r. per dose. Real eczemas on other parts of the body are usually cured by appropriate diet and local treatment with salves, so that radiation is seldom necessary. Thorium X is sometimes efficacious in cases in which roentgen is not. This method of radiation is to be employed particularly in neurodermitis with its classical localizations (cubital areas, etc.); and preferably as Thorium X—alcohol with 1,000 electrostatic units per cubic centimeter. The repeatedly painted skin site is covered with a thin layer of collodion. Because of possible after-effects, it is advisable not to undertake a second application of Thorium X before four to five weeks have elapsed. In children the author advises against the grenz ray therapy, for the present at any rate.

The Occupational Skin Diseases. Cause, Proof, and Expert Opinion. Bering, Fr., and Zitzke, E.: Leipzig, 1935. L. Voss.

The authors divide their book into two parts. Part I, general and definitions. Eczema is discussed as the commonest occupational disease; and in connection with this, allergy and sensitization. There is a discussion of individual idiosyncrasy and of polyvalent hypersensitivities, and their evaluation in damage suits. Then follows a description of the technic of skin testing. Tests must be made only with substances actually employed, not with substances bearing the same name. The history is often important in final decision of damage claims. Positive tests are decidedly stronger proofs than negative

results, particularly when the latter persist in contradiction to the course of the disease. There is included practical advice on matters of insurance and of prophylaxis. Part II consists of 45 sections discussing as many groups of occupations. The working conditions and hazards are clearly brought out and the chemistry is fully discussed. Many helpful examples are given in detailed histories and expert opinions. The difficulties of the whole complex question are most clearly illustrated. As a supplement, quite a comprehensive table of concentrations for skin testing is given. [Patch test concentration tables.]

The Irritants in Adhesive Plaster. Schwartz, Louis, and Peck, Samuel M.: Public Health Rep. 811-819, 1935.

After testing, the patients can be divided into three classes, as follows: (1) reaction after the first application (two days' duration) and increased reaction at the second inspection, two days after removal of the plaster; (2) negative reaction with late reaction at the second inspection; (3) no reaction, except erythema reddening at the site of the plaster. The skin manifestations can be placed in groups: (1) erythema, or, as result of direct irritation, vesicles and edema; (2) evidences of hypersensitivity (clinical picture of a dermatitis or eczema) to one or more of the component parts of the plaster. The manifestations of the first group disappear soon after removal of the plaster, while those of the second group persist several days. Resins, rubber, and pitch were found to be the chief irritants.

Concerning Occupational Acneform Skin Disease Due to Machine Oil. Kumashiro, M.: Nagasaki Igakkwai Zassi **13**: 857, 1935.

The author observed three cases of acneform follicular skin manifestations obviously due to machine oil. He then examined 100 fishing-boat engineers and found 90 per cent showing similar skin alterations. The principal site of the dermatosis was where body had been in contact with oil-soaked underwear. The primary manifestation is an acneform or lichenoid hyperkeratosis of the follicle, which becomes, through involution, a brownish pigmented spot with a central depression, or a sharply demarcated scar. Patch-testing healthy persons with machine oil elicited similar reactions. In conclusion there is brief comparison between tar or pitch skin and lubricating-oil skin. These three dermatoses can be differentiated only in degree and are fundamentally identical.

The Two Types of Allergic Skin Reaction. Tezner, Otto: Klin. Wchnschr. **14**: 539, 1935.

Tezner reports that, regardless of the degree of immunity of the organism, intracutaneous injections elicit two skin reactions, differing

chiefly as to time: (1) the immediate reaction—reddening, wheal formation, usually disappearing after one hour; (2) the late reaction—reddening and moderate tissue infiltration, reaching its maximum only after twenty-four hours and usually persisting several days. Both reactions can be considered as different degrees of sensitization. Experiments showed that when a normal child is sensitized with small doses, parenterally, at daily intervals, the following stages of skin reactions are observed in this order: intracutaneous late reaction, intracutaneous immediate reaction plus late reaction, and then intracutaneous immediate reaction and no late reaction. [Late reaction = tuberculin type reaction.]

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

The Occurrence of Eosinophiles in the Secretions From the Nose, the Sinuses and the Tonsils. Kallós, P.: Acta oto-laryng. **22**: 107, 1935.

Kallós made a study of 125 cases of nasal and tonsillar diseases in which the secretions were examined for eosinophiles. In the nasal cases, consisting of vasomotor rhinitis and nasal polyps, eosinophiles were found to be present in the secretions from 10 to 50 per cent. An eosinophilia was also demonstrated in secretions expressed from the tonsils in rheumatic patients. Definite eosinophilia was also demonstrated in the tonsils upon histologic examination. Similar studies in nonrheumatic patients revealed no eosinophilia. Kallós suggests a possible association between the tonsils and rheumatism on the basis of the local eosinophilia. These findings also suggest, perhaps, the allergic basis of rheumatism.

The Usefulness of Nasal Symptoms in Hay Fever. Benjamins, C. E., and de Graaf, J.: Acta oto-laryng. **20**: 165, 1934.

In a study of the nature of the local nasal reaction concerned in hay fever, Benjamins and de Graaf carried out a series of experiments. They concerned a comparative examination of the sensitivity of the skin, the nasal mucosa, and the conjunctiva to the active substance of pollen. The problem also concerned the investigation of the absorption of the active substance by the nasal mucosa and also the quantity of pollen likely to be found in the nose during the period of pollination of grasses. As a result of the experiments, it was shown that the skin is generally much more sensitive to the active principle of pollen than the nasal mucosa, but the absorption of the active substance by the

nasal mucosa can take place sufficiently to provoke general symptoms. It was also found that by using an artificial nose the quantity of pollen collected during the grass season is sufficient to produce general reactions upon absorption. It was concluded that the defensive reaction of the nasal mucosa, however, prevents the alarming symptoms that might occur from absorption of pollen. It was noted that the nasal mucosa in hay fever patients would react in the presence of 35 grains of pollen. In more sensitive cases, reactions occurred from a lesser number. The rhinorrhea and sneezing, therefore, are considered as playing an important part in the defense mechanism by eliminating excessive contact with pollen. It was finally concluded that the nasal symptoms of hay fever, although uncomfortable to the patient, serve a useful purpose and are indispensable.

Chemical and Physicochemical Examinations of Polyps in Cases of Nasal Disease and Asthma. Griebel, C. R.: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **138**: 178, 1934.

In 387 asthmatic patients examined by Griebel, it was found that 293 presented evidence of the allergic form of the disease. The pathologic conditions in the nose varied from the presence of simple serous fluid to marked polyposis. Chronic suppuration was found in 176 of 293 patients. This incidence of chronic suppuration is much higher than that noted by other observers. Physicochemical examinations made of nasal polyps revealed a relatively high mineral content and a hydrogen ion concentration of from 7.52 to 8.3. It was concluded that albumin plays a decisive part as the hydrophilic colloid in the development of polyps.

The Treatment of Chronic Sinus Infection With Undenatured Bacterial Antigens. Kracaw, F. C.: Laryngoscope **46**: 26, 1936.

In the more recent rhinologic literature, a number of reports have been presented on the local immunization of the nasal mucosa with varying results. Kracaw suggests that failures resulting from vaccine treatment are the result of the alterations of the bacterial antigenic complexes in the process of preparation of the vaccines. His observations were based upon the principles of vaccine preparation previously reported by Krueger by which the major antigenic substances of the bacteria are preserved in such a way as to prevent deterioration. The technic of preparing these bacterial antigens was outlined. Kracaw suggested the use of local and also general immunization in cases of allergic rhinitis of probable bacterial origin. He also advocated their use in chronic ethmoiditis, chronic sphenoiditis, and also in cases of chronic infection of the frontal sinuses.

In a previously reported series of 45 cases a year or more after completion of treatment, it was found that 28 of the 30 patients considered cured had maintained that status and 13 patients classified as presenting satisfactory clinical improvement all remained in this category. A second group comprising 62 patients showed 52 markedly improved or cured, 2 failures, and 8 patients in whom improvement was only moderate. It was finally concluded that topical and general immunization with undenatured bacterial antigens prepared according to the technic outlined is the method of choice for the treatment of chronic sinusitis.

Notes on a Case of Membranous Rhinitis Associated With Allergy. Kelly, D. B.: J. Laryng. & Otol. **50**: 444, 1935.

A very interesting case of membranous rhinitis associated with nasal allergy was reported by Kelly. The patient had had hay fever and was also known to be hypersensitive to horse dander. Examination of the nose showed a large, somewhat adherent gelatinous exudate which had a tendency to recur after removal. Its appearance was very suggestive of the type of membrane noted in diphtheria. A pathologic examination of the exudate, however, showed it to be markedly infiltrated with eosinophiles. A few common organisms were also noted but were not considered of significance. The occurrence of this type of membrane is occasionally noted in patients during the hay fever season but may also occur outside the hay fever season as a result of severe acute allergic exacerbations. We have observed a number of cases of this type in children.

Pediatrics

UNDER THE DIRECTION OF FRANCIS S. SMYTH, M.D., SAN FRANCISCO

The Evolution of Atopic Dermatitis. Hill, L. W., and Sulzberger, M. B.: Arch. Dermat. & Syph. **32**: 451, 1935.

The authors trace the atopic dermatitis through the stages of infantile eczema, neurodermatitis of childhood, and the final picture as seen in the adult. Quite logically they dispense with the burden of nomenclature, and show by individual case studies the desirability of more complete correlation. They believe that about half the cases show hereditary predisposition. They discuss such factors as Ratner's placental transmission of sensitivity. They avoid any discussion of the often observed disappearance of skin manifestations of infantile eczema or factors which tend to perpetuate the skin manifestations in some instances.

Dietetic Treatment of Neurodermatitis of Childhood. Schiff, E.: Arch. Pediat. **52**: 44, 1935.

This report, given as a lecture before the Bronx Hospital staff, offers an interesting contrast to the report of Hill and Sulzberger. With the different approach and apparently slight acquaintance with American studies in allergy, Professor Schiff advocates the use of a raw vegetable and fruit diet. Even for a three-year-old child radishes and cucumbers are included in the menus. He admits empiricism and is most pessimistic about our present knowledge.

Changes in the Blood and Functions of the Skin in Eczema. Fedoseqicz: Przegl. dermat. **29**: 27, 1934.

This investigator studied the eosinophilia, the hemoglobin, and the reactions to staphylococcus and streptococcus extracts. There was no consistent eosinophilia, and the hemoglobin was frequently low. Late cutaneous reactions were often stronger than those which developed early.

Allergic Enuresis. Bray, G. W.: Brit. J. Child. Dis. **32**: 136, 1935.

This is a convincing report of enuresis and papular urticaria in a girl of six years. There was a strong familial history of allergy. Skin reactions were positive to pork and pork products. Successful treatment consisted of eliminating the offending food and the use of ephedrine.

Cold Urticaria in Three Sisters. Kobacker, J. L., and Parkhurst, H. J.: J. A. M. A. **105**: 662, 1935.

Typical cold urticaria developed in three siblings following measles. There was no hereditary allergy.

A Case of Physical Allergy. Bray, G. W.: Brit. J. Child. Dis. **32**: 45, 1935.

Exposure to cold produced an erythematous and edematous change in the skin of a seven-year-old child. Marked prurigo was also present. There was a local eosinophilia at the site of the reaction. Histamine was used for treatment.

Allergy to Adhesive Tape. Slesinger, H. A.: Arch. Pediat. **52**: 715, 1935.

Two patients, aged eleven months and three years, respectively, developed dermatitis from adhesive tape.

Miscellaneous

Food Allergy and Other Factors in Angina Pectoris. Werley, G.: Southern M. J. **28**: 1156, 1935.

In 135 cases of angina pectoris and cardiac infarct the author detected a history of allergy in 93 per cent. In this group of cases food idiosyncrasies were found in 47 per cent, migraine in 35 per cent, urticaria in 17 per cent, hay fever in 12 per cent, and asthma in 95 per cent. These, the author points out, are far higher than occur in the general community. Case reports are given to exemplify the close relationship between angina pectoris and allergic disorders. Dietary elimination brought relief in many cases.

Experimental Studies on Calcium Therapy in Allergic Conditions. Kallos, P., and Kallos-Deffner, K.: Klin. Wchnschr. **14**: 1247, 1935.

The authors observed favorable results in various cases of allergy in calcium therapy. They investigated the possibility of the effect of calcium on the antigen antibody reaction. In using the Dale technic with isolated uterine strips of guinea pigs sensitized to horse serum, suspended in Ringer's solution, they observed that calcium gluconate exerts no harmful effect on the sensitized muscle strips even if used in strong doses over long periods of time. When horse serum is added to the sensitized muscle strips, contraction does not develop in the presence of sufficient amounts of calcium. The simultaneous administration of horse serum and calcium leads to desensitization of the strips, and existing anaphylactic contraction of the muscle strip can be released instantaneously by the addition of calcium. The authors maintain that the results of these experiments indicate that calcium therapy of allergic conditions is well founded.

The Occurrence of So-called Latent Allergy. Salen, E. B., and Juhlin-Dannfelt: Acta Med. **86**: 505, 1935.

The authors tested 432 individuals belonging to different occupational groups (bakers, veterinarians, garment workers, etc.) with various allergens encountered in the occupation in order to determine the incidence of sensitization to such allergens and also how often manifest allergy follows these reactions. It was found that those exposed to occupational allergens reacted to these on skin tests far more frequently than controls, who were in different occupational groups. These results indicate to the authors that a positive skin test to allergens to which one is exposed even if no symptoms are present implies latent allergy. This is present in an appreciable number of indi-

viduals. A discussion of the mechanism by which these reactions occur brings out that absorption probably takes place through intact mucous membranes and skin. The authors formulate the question why some sensitized persons have clinical allergy and others not, rather than why some become sensitive, since they believe most individuals with sufficient exposure will become sensitized.

Hypersensitiveness to Pituitary Extracts. Simon, F. M., and Ryder, C. F.: J. A. M. A. **106**: 512, 1936.

In a period of less than two years, five cases of hypersensitiveness to pituitary extract have been observed in the Louisville City Hospital. Three of these occurred within three months. Sensitiveness was manifested by urticaria, angioneurotic edema, and respiratory difficulty relieved by epinephrine. All had had previous injections of pituitary extract. Skin tests made with various preparations were positive with various brands of extracts and their derivatives, showing that sensitization is not limited to one particular preparation. Pitocin, containing the oxytocic factor, gave negative tests; while pitressin, containing the vasoconstrictor and antidiuretic principles, gave positive tests. All extracts gave negative tests on normal controls. Patients who react have a high degree of sensitivity compared to that seen in hay fever. Passive transfer was secured in two of the cases.

The results of these observations indicate that the hypersensitiveness is organ specific and is directed toward some constituent of the pituitary gland of several species including man. This constituent is neither vasopressor nor oxytocic principle.

The Treatment of Intractable Urticaria by Ionization With Histamine. Fiessinger, N., and Gajdus, A.: Presse méd. **95**: 1913, 1935.

The authors report six cases of urticaria, the duration of which varied from a few months to some years. Iontophoresis with histamine brought marked relief. The technic of treatment consists of a compress moistened with an aqueous solution of histamine hydrochloride 1:10,000 placed on the skin of the epigastric region. The compress is covered by an aluminum plate to which the positive pole of the source of a galvanic current is attached. From 6 to 10 milliamperes are passed through the circuit for five to ten minutes, the indifferent electrode being held in the patient's hand. There are no known contraindications. The action on gastric acid is insignificant. The treatment must be repeated 10 or 12 times to secure proper results.

The Relationship of the Eosinophile Leucocyte to Allergy and Anaphylaxis. Campbell, A. C. P., Drennan, A. M., and Rettie, T.: J. Path. & Bact. **40**: 537, 1935.

In guinea pigs, allergic inflammation is frequently although not constantly associated with a local or general eosinophilia. Unless an allergic reaction is present, local eosinophilia does not occur after injection of a foreign protein. Likewise, blood eosinophilia is produced after reinjection only under circumstances which conform to allergy, namely, an interval of time following the first injection which corresponds to that necessary for the development of sensitization. Preexisting blood eosinophilia appears to have no protective action against the development of allergy or general anaphylaxis.

Cortin Protection Against Anaphylactic Shock in Guinea Pigs. Wolfram, J., and Zwemer, R. L.: J. Exper. Med. **61**: 9, 1935.

Crystallized egg albumen was injected into 49 guinea pigs. Two weeks later a second dose was given to 16 control animals, and but 2 survived. Of the remaining animals, 16 received cortin from two to six hours before the shocking dose and 9 survived. The remaining cortin-treated animals received the hormone at other time intervals, and protection was inconclusive in this group. Two weeks after the first test the cortin-treated survivors succumbed to another dose of antigen which on this occasion was not preceded by cortical extract.

Studies on the Sensitization of Animals With Simple Chemical Compounds. Landsteiner, K., and Jacobs, J.: J. Exper. Med. **61**: 643, 1935.

Sensitization of guinea pigs was accomplished by the administration of minute amounts (fractions of milligrams) of 1:2:4 chlorodinitrobenzene, P-nitrosodimethylaniline, 1:2:4 trinitrobenzene, picrylchloride, four dichlorodinitro-benzenes, and a number of other aromatic compounds. Several similar substances gave negative results. Chlorodinitrobenzene is known to produce hypersensitiveness in man, a large number of cases having been observed in factory workers. The mechanism of such sensitization is discussed.